A CROSS SECTIONAL STUDY ON SUBCLINICAL HYPOTHYROIDISM IN ELDERLY FEMALES ABOVE THE AGE OF FIFTY YEARS

submitted to
The Tamil Nadu Dr.M.G.R.Medical University

M.D. DEGREE EXAMINATION
BRANCH – I (GENERAL MEDICINE)

GOVT. CHENGALPATTU MEDICAL COLLEGE & HOSPITAL

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

APRIL 2013

BONAFIDE CERTIFICATE

This is to certify that the dissertation titled "**A CROSS SECTIONAL STUDY ON SUBCLINICAL HYPOTHYROIDISM IN ELDERLY FEMALES ABOVE THE AGE OF FIFTY YEARS**" is a bonafide work done by Dr.RAMKUMAR.S, post graduate student, Department of General Medicine, Chengalpattu Medical College, Chengalpattu, under my guidance and supervision in partial fulfillment of regulations for M.D. Degree Branch I (General Medicine) examination of the **Tamil Nadu Dr. M.G.R Medical University** to be held in APRIL 2013. The period of study was from OCTOBER 2010 to OCTOBER 2012.

PROF. DR.K.E.ARUMUGAM, M.D

HOD, DEPT OF MEDICINE

PROF. DR. P.R.THENMOZHI VALLI, M.D
DEAN

CHENGALPATTU MEDICAL COLLEGE & HOSPITAL

Place : Chengalpattu Date :

DECLARATION

I, Dr. RAMKUMAR. S hereby solemnly declare that the dissertation titled, **"A CROSS SECTIONAL STUDY ON SUBCLINICAL HYPOTHYROIDISM IN ELDERLY FEMALES ABOVE THE AGE OF FIFTY YEARS"** was done by me at GOVT. CHENGALPATTU MEDICAL COLLEGE & HOSPITAL from OCTOBERER 2010 to OCTOBER 2012 under the supervision and guidance of my Unit Chief **Prof**. **DR**. **R. JAYANTHI, M.D.,** This dissertation is submitted to Tamil Nadu DR. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch -I) in General Medicine.**

Place: CHENGALPATTU.

Date: (DR. RAMKUMAR. S)

Ref.No.2508/MEI/2010

Office of the Dean,
Chengalpattu Medical College,
Chengalpattu – 603 001.

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Sub: Medical Education – Chengalpattu Medical College, Chengalpattu – Dr.S.Ramkumar, Post Graduate Student in M.D.(General Medicine) – Admitted during the Academic year 2010-2011 – Dissertation submitted for the Approval of the Human Ethical Committee for the study work entitled **"A Cross Sectional Study on Subclinical Hypothyroidism in Elderly Females above the Age of Fifty Years" - Approved - Orders - Issued.**

Ref: 1) Application dated: 27.03.2012f the Individual.
2) Letter dated 27.03.2012 of the Head of the Department of General Medicine, Chengalpattu Medical College,Chengalpattu.

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Dr.S.Ramkumar, Post Graduate Student in M.D.(General Medicine) of this college has submitted a Dissertation for the study work entitled "A Cross Sectional Study on Subclinical Hypothyroidism in Elderly Females above the Age of Fifty Years . The Study of the above individual has been approved by the Human Ethical Committee of the Chengalpattu Medical College, Chengalpattu which is forwarded herewith for further course of action.

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DEAN INCHARGE

Encl.: Copy of the Dissertation Study Work.

20/6/12

To
Dr.S.Ramkumar,
P.G.Student in M.D.(General Medicine),
Chengalpattu Medical College, Chengalpattu. .. through the H.O.D. of General Medicine.

Copy to:
1)The Director of Medical Education, Chennai – 10.
2) The Controller of Examinations,
The Tamil Nadu Dr.M.G.R.Medical University, Chennai - 32.
3)The Head of the Department of General Medicine,
Chengalpattu Medical College, Chengalpattu – 603 001.
4)ME II Section through the Office Superintendent (ME).

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INTRODUCTION

The term subclinical hypothyroidism was originally used to describe the patient with a low- normal free T4 but a slightly elevated serum TSH level. Other terms for this condition are mild hypothyroidism early thyroid failure, preclinical hypothyroidism, and decreased thyroid reserve. The TSH elevation in such patients is modest, with values typically between 4 and 15 mU/L, although patients with a TSH above 10 mU/L more often have a reduced free T4 and may have some hypothyroid symptoms. The definition of this syndrome depends significantly on the reference range for a normal TSH concentration. This syndrome is most often seen in patients with early Hashimoto's disease and is a common phenomenon, occurring in 7% to 10% of older women.[1,2,3] The common etiology of this disease are not sufficiently treated cases of hypothyroidism and disease of the gland caused by autoimmunity. The existence of antibodies against the gland point out the existence of autoimmune disease of the gland. Other etiologies for this disease are those cases of hyperthyroidism who have undergone therapy in the past, those who have undergone radiation treatment to the neck in the past and also undergone therapy like with cytokines, therapy with iodine, therapy with lithium, with drugs like amiodarone and also the thyroiditis which develops after delivery which has got a hypothyroid period [4]. Subclinical hypothyroidism is very commonly encountered in the community showing a prevalence rate of three to eight percent

where previously no disease of the thyroid has been shown to occur [2,5]. There is a rise seen in the prevalence as the age progresses and also more case is seen in females.[2]

Also prevalence of subclinical hypothyroidism is more in females than in males and also in older people than in younger people because of the fact that the prevalence of thyroglobulin and thyroid peroxidase (microsomal) antibodies is higher in females and in older people. Subjects due to subclinical hypothyroidism show an increased rate at which they convert into clinical hypothyroidism about 2.6 % every year in cases when the thyroperoxidase have antibodies against them not present and 4.3 percent if they have it [6]. However it has been shown that some people do not manifest clinical hypothyroidism while others return to normal level.

A thyroid stimulating hormone value more than 10 mIU/L mostly manifest clinical hypothyroidism while value below 6 mIU/L less frequently manifest. It has been shown in one of the trials in both males and females above fifty five years and followed up for a mean period of thirty two months, the thyroid stimulating hormone values returned to normal in fifty two percent of subjects who had the hormone below 10 mIU/L[7]. Even though it has been agreed that hypothyroidism results in increase in the cholesterol levels in the patient there by causing atherosclerosis[8], it has been found out from various studies that the correlation between increased lipids, atherosclerosis and subclinical hypothyroidism resulted

in not so convincing outcome. While some studies showed that there are large number of hypercholesterolemic patients in SH while some other studies showed that SH patients develop only modest in the range of only 10% higher average in terms of total cholesterol than subjects not having the disease [9-22]. In the first Whickham study it was shown that the cholesterol levels did not show any association with regard to the increase in thyroid stimulating hormone after the researchers adjusted the subjects for age [11]. Also after that the Whickham survey showed that there is no relation between the increased thyroid stimulating hormone and increased probability of suffering from ischemic disease of the heart or abnormality in serum lipid levels [23]. Therefore it can be said that from the discussions above the relationship between subclinical hypothyroidism and cardiovascular disease remains controversial. However there was no difference between women with subclinical hypothyroidism and controls regarding hypertension and diabetes mellitus [21,24]. This study was done to find out the prevalence of subclinical hypothyroidism and its relation to Hypertension, Diabetes and Ischemic heart disease among women above the age of 50 years attending medical outpatient clinic at Government chengalpattu medical college and hospital.

AIM OF THE STUDY

• To find out the prevalence of subclinical hypothyroidism among women above 50 years of age.

• To study the relation between subclinical hypothyroidism and Hypertension, Diabetes and Ischemic Heart Disease in those patients.

REVIEW OF LITERATURE

PHYLOGENY, EMBRYOLOGY, AND ONTOGENY [25]

Phylogeny

The phylogeny, embryogenesis, and certain aspects of thyroid function are closely interlinked with the gastrointestinal tract. Monoiodotyrosine (3'-monoiodo-l-tyrosine [MIT]) and diiodotyrosine (3,5'-diiodo-l-tyrosine [DIT]) are present in a variety of invertebrate species, including mollusks, crustaceans, coelenterates, annelids, insects, and certain marine algae. In these lower forms, however, no recognizable thyroid tissue is present. Thyroid gland is found in all vertebrates and confined to them. Other glands which concentrate iodide in their secretions are the gastric and salivary glands.

Structural Embryology

The human thyroid anlage is first recognizable at E16-17. The thyroid gland develops from the floor of the primitive pharynx during the third week of gestation. The developing gland migrates along the thyroglossal duct to reach its final location in the neck. Thyroid hormone synthesis normally begins at about 11 weeks' gestation. Neural crest derivatives from the ultimobranchial body give rise to thyroid medullary C cells that produce calcitonin, a calcium-lowering hormone.The C cells are interspersed throughout the thyroid gland, although their

density is greatest in the juncture of the upper one-third and lower two-thirds of the gland.Thyroid gland development is orchestrated by the coordinated expression of several developmental transcription factors. Thyroid transcription factor (TTF)-1, TTF-2, and paired homeobox-8 (PAX-8) are expressed selectively, but not exclusively, in the thyroid gland. In combination, they dictate thyroid cell development and the induction of thyroid-specific genes such as thyroglobulin (Tg), thyroid peroxidase (TPO), the sodium iodide symporter (Na^+/I, NIS), and the thyroid-stimulating hormone receptor (TSH-R).

Functional Ontogeny

The ontogeny of thyroid function and its regulation in the human fetus are fairly well defined. Future follicular cells acquire the capacity to form thyroglobulin (Tg) as early as the 29th day of gestation, whereas the capacities to concentrate iodide and synthesize thyroxine (T4) are delayed until about the 11th week. Radioactive iodine inadvertently given to the mother would be accumulated by the fetal thyroid soon thereafter. Early growth and development of the thyroid do not seem to be TSH-dependent, because the capacity of the pituitary to synthesize and secrete TSH is not apparent until the 14th week. Subsequently, rapid changes in pituitary and thyroid function take place. Probably as a consequence of hypothalamic maturation and increasing secretion of thyrotropin-releasing hormone (TRH), the serum TSH concentration increases between 18 and 26 weeks' gestation, after

which levels remain higher than those in the mother. The higher levels may reflect a higher set-point of the negative feedback control of TSH secretion during fetal life than at maturity. Thyroxine-binding globulin (TBG), the major thyroid hormone–binding protein in plasma, is detectable in the serum by the 10th gestational week and increases in concentration progressively to term. This increase in TBG concentration accounts in part for the progressive increase in the serum T4 concentration during the second and third trimesters, but increased secretion of T4 must also play a role because the concentration of free T4 also rises. Several aspects of thyroid development are of note from the clinical standpoint. Rarely, thyroid tissue may develop from remnants of the thyroglossal duct near the base of the tongue. Such lingual thyroid tissue may be the sole functioning thyroid present and, thus, its surgical removal will lead to hypothyroidism. More commonly, elements of the thyroglossal duct may persist and later give rise to thyroglossal duct cysts, or ectopic thyroid tissue may be present at any location in the mediastinum or, rarely, even in the heart.

ANATOMY AND HISTOLOGY [26]

The number of lobes in the gland is two and they are joined by a piece of the gland called the isthmus. The gland is present in front of the trachea. It is situated in the neck with the cricoid at the top and down below is suprasternal notch. The gland usually weighs about twelve to twenty grams.The superior and inferior thyroid

artery supplies blood. There are 4 parathyroid glands, the source of parathyroid hormone and are situated behind the gland's poles. One important structure which needs to be watched carefully during surgery of the gland is recurrent laryngeal nerve which courses by the side of the gland and they are frequently injured leading to the paralysis of the cord. The thyroid gland consists of numerous spherical follicles composed of thyroid follicular cells that surround secreted colloid, a proteinaceous fluid containing large amounts of thyroglobulin, precursor of thyroid hormones. The thyroid follicular cells are polarized—the basolateral surface is apposed to the bloodstream and an apical surface faces the follicular lumen. Increased demand for thyroid hormone is regulated by thyroid-stimulating hormone (TSH), which binds to its receptor on the basolateral surface of the follicular cells, leading to Tg reabsorption from the follicular lumen, proteolysis within the cytoplasm, yielding thyroid hormones for secretion into the bloodstream.

IODINE AND THE SYNTHESIS AND SECRETION OF THYROID [26] HORMONES

Thyroid Hormone Synthesis

The hormones of the gland are made from thyroglobulin. After thyroglobulin is poured into follicles of the gland, iodine is attached to tyrosine residues and these

are joined by ether linkage. When the thyroglobulin is once again taken back into the follicles of the gland and proteolysis occurs and the newly made T4, T3 are released.

Iodine Metabolism and Transport

One of the first important steps in the production of thyroid hormone is taking up of the iodide. The iodine which we take through diet is attached to the proteins present in the serum, mainly albumin. The iodine which is not bound gets out of the body in urine. The iodine present in the blood is efficiently caught by the gland. Sodium/iodine symporter (NIS) which carries out the process of taking up the iodide is present in basolateral membrane in the follicles of the gland. NIS is mainly found in thyroid but less of it is found in structures like salivary gland, milk secreting mammary glands and placenta. The presence of less iodine results in more NIS being expressed, whereas high iodine levels suppress NIS expression and uptake. The selective expression of NIS in the thyroid allows isotopic scanning, treatment of hyperthyroidism, and ablation of thyroid cancer with radioisotopes of iodine, without significant effects on other organs. Mutation of the NIS gene is a rare cause of congenital hypothyroidism, underscoring its importance in thyroid hormone synthesis. Another iodine transporter, pendrin, is located on the apical surface of thyroid cells and mediates iodine efflux into the lumen. Mutations of the pendrin gene causes pendred syndrome, a disorder characterized by

defective organification of iodine, goiter and sensorineural deafness. Iodine deficiency is prevalent in many mountainous regions. The World Health Organization (WHO) estimates that about 2 billion people are iodine-deficient, based on urinary excretion data. In areas of relative iodine deficiency, there is an increased prevalence of goiter and, when deficiency is severe, hypothyroidism and cretinism. Cretinism is characterized by mental and growth retardation and occurs when children who live in iodine-deficient regions are not treated with iodine or thyroid hormone to restore normal thyroid hormone levels during early life. These children are often born to mothers with iodine deficiency, and it is likely that maternal thyroid hormone deficiency worsens the condition. Concomitant selenium deficiency may also contribute to the neurologic manifestations of cretinism. Iodine supplementation of salt, bread, and other food substances has markedly reduced the prevalence of cretinism. Unfortunately, however, iodine deficiency remains the most common cause of preventable mental deficiency, often because of societal resistance to food additives or the cost of supplementation. In addition to overt cretinism, mild iodine deficiency can lead to subtle reduction of IQ. Oversupply of iodine, through supplements or foods enriched in iodine (e.g., shellfish, kelp), is associated with an increased incidence of autoimmune thyroid disease. The recommended average daily intake of iodine is 150–250 μg/d for

adults, 90–120 μg/d for children, and 250 μg/d for pregnant and lactating women. Urinary iodine is >10 μg/dL in iodine-sufficient populations.

Organification, Coupling, Storage, Release

After iodide enters the thyroid, it is trapped and transported to the apical membrane of thyroid follicular cells, where it is oxidized in an organification reaction that involves TPO and hydrogen peroxide. The reactive iodine atom is added to selected tyrosyl residues within Tg. The iodotyrosines in Tg are then coupled via an ether linkage in a reaction that is also catalyzed by TPO. Either T4 or T_3 can be produced by this reaction, depending on the number of iodine atoms present in the iodotyrosines. After coupling, Tg is taken back into the thyroid cell, where it is processed in lysosomes to release T_4 and T_3. Uncoupled mono- and diiodotyrosines (MIT, DIT) are deiodinated by the enzyme dehalogenase, thereby recycling any iodide that is not converted into thyroid hormones. Disorders of thyroid hormone synthesis are rare causes of congenital hypothyroidism. The vast majority of these disorders are due to recessive mutations in TPO or Tg, but defects have also been identified in the TSH-R, NIS, pendrin, hydrogen peroxide generation, and dehalogenase. Because of the biosynthetic defect, the gland is incapable of synthesizing adequate amounts of hormone, leading to increased TSH and a large goiter.

TSH Action

TSH regulates thyroid gland function through the TSH-R, a seven-transmembrane G protein–coupled receptor (GPCR). The TSH-R is coupled to the subunit of stimulatory G protein (G_s), which activates adenylyl cyclase, leading to increased production of cyclic AMP. TSH also stimulates phosphatidylinositol turnover by activating phospholipase C. The functional role of the TSH-R is exemplified by the consequences of naturally occurring mutations. Recessive loss-of-function mutations cause thyroid hypoplasia and congenital hypothyroidism. Dominant gain-of-function mutations cause sporadic or familial hyperthyroidism that is characterized by goiter, thyroid cell hyperplasia, and autonomous function. Most of these activating mutations occur in the transmembrane domain of the receptor. They mimic the conformational changes induced by TSH binding or the interactions of thyroid-stimulating immunoglobulins (TSI) in Graves' disease. Activating TSH-R mutations also occur as somatic events, leading to clonal selection and expansion of the affected thyroid follicular cell and autonomously functioning thyroid nodules.

Other Factors playing a role in hormone production and it’s release

Although TSH is the dominant hormonal regulator of thyroid gland growth and function, a variety of growth factors, most produced locally in the thyroid gland,

also influence thyroid hormone synthesis. These include insulin-like growth factor I (IGF-1), epidermal growth factor, transforming growth factor (TGF-), endothelins, and various cytokines. The quantitative roles of these factors are not well understood, but they are important in selected disease states. Certain cytokines and interleukins (ILs) produced in association with autoimmune thyroid disease induce thyroid growth, whereas others lead to apoptosis. In acromegaly, increased levels of growth hormone and IGF-1 are associated with goiter and predisposition to multinodular goiter (MNG). Iodine deficiency increases thyroid blood flow and upregulates the NIS, stimulating more efficient iodine uptake. Excess iodide transiently inhibits thyroid iodide organification, a phenomenon known as the Wolff-Chaikoff effect. In individuals with a normal thyroid, the gland escapes from this inhibitory effect and iodide organification resumes; the suppressive action of high iodide may persist, however, in patients with underlying autoimmune thyroid disease.

Thyroid Hormone Transport and Metabolism [26]

SERUM BINDING PROTEINS

T4 is secreted from the thyroid gland in about twentyfold excess over T_3. Both hormones are bound to plasma proteins, including thyroxine-binding globulin (TBG), transthyretin (TTR, formerly known as thyroxine-binding prealbumin, or

TBPA), and albumin. The plasma-binding proteins increase the pool of circulating hormone, delay hormone clearance, and may modulate hormone delivery to selected tissue sites. The concentration of TBG is relatively low (1–2 mg/dL), but because of its high affinity for thyroid hormones ($T_4 > T_3$), it carries about 80% of the bound hormones. Albumin has relatively low affinity for thyroid hormones but has a high plasma concentration (3.5 g/dL), and it binds up to 10% of T_4 and 30% of T_3. TTR carries about 10% of T_4 but little T_3. Approximately 99.98% of T4 and 99.7% of T_3 are protein-bound. Because T_3 is less tightly bound than T_4, the fraction of unbound T_3 is greater than unbound T_4, but there is less unbound T_3 in the circulation because it is produced in smaller amounts and cleared more rapidly than T_4. The unbound or "free" concentrations of the hormones are $2 \times 10^{11} M$ for T_4 and $6 \times 10^{12} M$ for T_3, which roughly correspond to the thyroid hormone receptor binding constants for these hormones. The unbound hormone is thought to be biologically available to tissues. Nonetheless, the homeostatic mechanisms that regulate the thyroid axis are directed toward maintenance of normal concentrations of unbound hormones.

DEIODINASES

T4 may be thought of as a precursor for the more potent T_3. T_4 is converted to T_3 by the deiodinase enzymes. Type I deiodinase, which is located primarily in thyroid, liver, and kidneys, has a relatively low affinity for T_4. Type II deiodinase

has a higher affinity for T_4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. Expression of type II deiodinase allows it to regulate T_3 concentrations locally. Type II deiodinase is also regulated by thyroid hormone; hypothyroidism induces the enzyme, resulting in enhanced T_4 to T_3 conversion in tissues such as brain and pituitary. T_4 to T_3 conversion is impaired by fasting, systemic illness or acute trauma, oral contrast agents, and a variety of medications (e.g., propylthiouracil, propranolol, amiodarone, glucocorticoids). Type III deiodinase inactivates T_4 and T_3 and is the most important source of reverse T_3 (rT_3). Massive hemangiomas that express type III deiodinase are a rare cause of hypothyroidism in infants.

Thyroid Hormone Action [26]

THYROID HORMONE TRANSPORT

Circulating thyroid hormones enter cells by passive diffusion and via specific transporters such as the monocarboxylate 8 (MCT8) transporter. Mutations in the MCT8 gene have been identified in patients with X-linked psychomotor retardation and thyroid function abnormalities (low T4, high T_3, and high TSH). After entering cells, thyroid hormones act primarily through nuclear receptors, although they also have nongenomic actions through stimulating plasma membrane and mitochondrial enzymatic responses.

NUCLEAR THYROID HORMONE RECEPTORS

Thyroid hormones bind with high affinity to nuclear thyroid hormone receptors TRs) α and β. Both TR α and TR β are expressed in most tissues, but their relative expression levels vary among organs; TR α is particularly abundant in brain, kidneys, gonads, muscle, and heart, whereas TR β expression is relatively high in the pituitary and liver. Both receptors are variably spliced to form unique isoforms. The TR β2 isoform, which has a unique amino terminus, is selectively expressed in the hypothalamus and pituitary, where it plays a role in feedback control of the thyroid axis. The TR α2 isoform contains a unique carboxy terminus that precludes thyroid hormone binding; it may function to block the action of other TR isoforms. The receptors contain a domain in the central region of DNA for binding and another region for binding in the C- terminal ligand. It results in binding to specific DNA sequences, termed thyroid response elements (TREs), in the promoter regions of target genes. The receptors bind as homodimers or, more commonly, as heterodimers with retinoic acid X receptors (RXRs). The activated receptor can either stimulate gene transcription (e.g., myosin heavy chain α) or inhibit transcription (e.g., TSH β -subunit gene), depending on the nature of the regulatory elements in the target gene. Thyroid hormones (T_3 and T4) bind with similar affinities to TR α and TR β. However, structural differences in the ligand binding domains provide the potential for developing receptor-selective agonists or

antagonists. T_3 is bound with 10–15 times greater affinity than T_4, which explains its increased hormonal potency. Though T_4 is produced in excess of T_3, receptors are occupied mainly by T_3, reflecting T_4 to T_3 conversion by peripheral tissues, greater T_3 bioavailability in the plasma, and receptors' greater affinity for T_3. After binding to TRs, thyroid hormone induces conformational changes in the receptors that modify its interactions with accessory transcription factors. Importantly, in the absence of thyroid hormone binding, the aporeceptors bind to co-repressor proteins that inhibit gene transcription. Hormone binding dissociates the co-repressors and allows the recruitment of coactivators that enhance transcription. The discovery of TR interactions with corepressors explains the fact that TR silences gene expression in the absence of hormone binding. Consequently, hormone deficiency has a profound effect on gene expression because it causes gene repression as well as loss of hormone-induced stimulation. This concept has been corroborated by the finding that targeted deletion of the TR genes in mice has a less-pronounced phenotypic effect than hormone deficiency.

THYROID HORMONE RESISTANCE

Resistance to thyroid hormone (RTH) is an autosomal dominant disorder characterized by elevated thyroid hormone levels and inappropriately normal or elevated TSH. Individuals with RTH do not, in general, exhibit signs and

symptoms that are typical of hypothyroidism because hormone resistance is partial and is compensated by increased levels of thyroid hormone. The clinical features of RTH can include goiter, attention deficit disorder, mild reduction in IQ, delayed skeletal maturation, tachycardia, and impaired metabolic responses to thyroid hormone. RTH is caused by mutations in the TR β receptor gene. These mutations, located in restricted regions of the ligand-binding domain, cause loss of receptor function. However, because the mutant receptors retain the capacity to dimerize with RXRs, bind to DNA, and recruit co-repressor proteins, they function as antagonists of the remaining normal TR β and TR α receptors. This property, referred to as "dominant negative" activity, explains the autosomal dominant mode of transmission. The diagnosis is suspected when unbound thyroid hormone levels are increased without suppression of TSH. Similar hormonal abnormalities are found in other affected family members, although the TR β mutation arises de novo in about 20% of patients. DNA sequence analysis of the TR β gene provides a definitive diagnosis. RTH must be distinguished from other causes of euthyroid hyperthyroxinemia and inappropriate secretion of TSH by TSH-secreting pituitary adenomas. In most patients, no treatment is indicated; the importance of making the diagnosis is to avoid inappropriate treatment of mistaken hyperthyroidism and to provide genetic counseling.

Physical Examination

In addition to the examination of the thyroid itself, the physical examination should include a search for signs of abnormal thyroid function and the extrathyroidal features of ophthalmopathy and dermopathy. Examination of the neck begins by inspecting the seated patient from the front and side and noting any surgical scars, obvious masses, or distended veins. The thyroid can be palpated with both hands from behind or while facing the patient, using the thumbs to palpate each lobe. It is best to use a combination of these methods, especially when nodules are small. The patient's neck should be slightly flexed to relax the neck muscles. After locating the cricoid cartilage, the isthmus can be identified and followed laterally to locate either lobe (normally, the right lobe is slightly larger than the left). By asking the patient to swallow sips of water, thyroid consistency can be better appreciated as the gland moves beneath the examiner's fingers. Features to be noted include thyroid size, consistency, nodularity, and any tenderness or fixation. An estimate of thyroid size (normally 12–20 g) should be made, and a drawing is often the best way to record findings. However, ultrasound is the method of choice when it is important to determine thyroid size accurately. The size, location, and consistency of any nodules should also be defined. A bruit over the gland indicates increased vascularity, as occurs in hyperthyroidism. If the lower borders of the thyroid lobes are not clearly felt, a goiter may be retrosternal. Large retrosternal goiters can

cause venous distention over the neck and difficulty breathing, especially when the arms are raised (Pemberton's sign). With any central mass above the thyroid, the tongue should be extended, as thyroglossal cysts then move upward. The thyroid examination is not complete without assessment for lymphadenopathy in the supraclavicular and cervical regions of the neck.

REGULATION OF THE THYROID AXIS [26]

TSH, secreted by the thyrotrope cells of the anterior pituitary, plays a pivotal role in control of the thyroid axis and serves as the most useful physiologic marker of thyroid hormone action. TSH is a 31-kDa hormone composed of α and β subunits. Hypothalamic TRH stimulates pituitary production of TSH, which, in turn, stimulates thyroid hormone synthesis and secretion. Thyroid hormones, acting predominantly through thyroid hormone receptor β2 (TR β 2), feed back to inhibit TRH and TSH production. The "set-point" in this axis is established by TSH. TRH is the major positive regulator of TSH synthesis and secretion. Reduced levels of thyroid hormone increase basal TSH production and enhance TRH-mediated stimulation of TSH. High thyroid hormone levels rapidly and directly suppress TSH gene expression secretion and inhibit TRH stimulation of TSH, indicating that thyroid hormones are the dominant regulator of TSH production. Like other

pituitary hormones, TSH is released in a pulsatile manner and exhibits a diurnal rhythm; its highest levels occur at night.

LABORATORY ASSESSMENT OF THYROID STATUS [25]

Tests of the Hypothalamic-Pituitary-Thyroid Axis

While an inherently indirect reflection of thyroid hormone supply, tests that assess the state of the hypothalamic-pituitary-thyroid axis play a critical role in the diagnosis of thyroid disease. This is because the rate of TSH secretion is exquisitely sensitive to the plasma concentrations of free thyroid hormones thus providing a precise and specific barometer of the thyroid status of the patient. Immunometric assay technology now makes it possible to define the normal range for serum TSH and hence to ascertain both when thyroid function is inadequate or when the hormone supply is excessive. This assay uses the TSH molecule as a link between a TSH antibody bound to an inert surface (e.g., particles, the side of a test tube) and a second antibody directed against a different TSH epitope that is labeled with a detectable marker (I 125, an enzyme, or a chemiluminescent reagent). Thus, the signal generated is proportional to the concentration of TSH in the serum. This technique is more specific, sensitive, and rapid than radioimmunoassay. The serum TSH normal range by immunometric assay differs slightly in different labs but is most commonly 0.4 to 4.2mU/L. It should be kept in mind that there is a diurnal

variation of TSH secretion with peak values in the early evening and a nadir in the afternoon. A borderline abnormal value should always be repeated within a period of a week or so to be certain that it is representative. A minimally suitable TSH assay should be able to quantitate concentrations of TSH of 0.1 mU/L with a coefficient of variation of less than 20%. TSH β-subunit is not detectable in serum but the α-subunit which is common to FSH, hCG, TSH and LH is detectable with a normal range of 1 to 5μg/L. When FSH and LH production are increased, as in postmenopausal women, or when TSH production is increased, as in primary hypothyroidism, the free a-subunit level is also increased. The a-subunit level may also be increased in patients with glycoprotein producing tumors of the anterior pituitary. Its measurement may be useful in the rare patient with hyperthyroidism and a normal or elevated TSH to differentiate between neoplastic and nonneoplastic causes of TSH excess.

TSH in Patients with Thyroid Dysfunction

Patients with thyrotoxicosis which is due to excess thyroid hormone from any cause and/or hyperthyroidism which is due to excess secretion of thyroid hormone will virtually be characterised by a subnormal TSH. Patients with pituitary or hypothalamic hypothyroidism is often characterised by a normal or even slightly elevated serum TSH. In general, the degree of TSH elevation correlates with the clinical severity of the hypothyroidism. Patients with serum TSH values in the

range of 5 to 15 mU/L have few if any symptoms,[27] and the serum free T4 or free T4 index (F T4I) is typically low-normal while serum free T3 concentrations are normal.[28] [29] Such individuals with modest TSH elevation are said to have subclinical hypothyroidism if the serum free T4 is in the normal range. An elevation in both serum TSH and free T4 is unusual and indicates either autonomous TSH production as with a TSH-secreting pituitary tumor, resistance to thyroid hormone (RTH), or hyperthyroidism with an artifactual elevation in TSH.

QUANTITATION OF SERUM THYROID HORMONE CONCENTRATIONS

Total T4 and T3

Quantitation of the circulating thyroid hormone concentrations is essential to confirm that the thyroid status abnormality suggested by an abnormal TSH result is accurate as well as documenting its severity. Sensitive and specific radioimmunoassays are available for measuring the total concentrations of T4 and T3 and some of their metabolic by-products. Because the thyroid status correlates with the free, rather than with the total, hormone concentration, the physician must also obtain some estimate of that. The degree of abnormality in the free T4 generally correlates with the severity of the hormone excess or deficiency, whereas the serum TSH concentration is an indication of the impact of this abnormality in

that specific patient. The normal range for serum T3 concentration is 1.1 to 2.9 nmol/L (70 to 190 ng/dL). The normal total T4 is 64 to 142 nmol/L (5 to 11 μg/dL).

Concentrations of Free T4 and T3.

The normal ranges for free T4 and T3 are 9 to 30 pmol/L (0.7 to 2.5 ng/dL) and for free T3, 3 to 8 pmol/L (0.2 to 0.5 ng/dL). Because T4 is the major secretory product of the thyroid and correlates most closely with the serum TSH, in most situations, a free T4 estimate is all that is required to ascertain the state of thyroid secretion or supply. An array of methods is used to quantitate free T4 (or T3) in whole serum using automated methods.[30] There are two general categories of methods: free T4 index methods and comparative free T4 methods. Three general approaches are used: (1) two-step labeled hormone methods, (2) one-step labeled analogue methods, and (3) labeled antibody approaches. In general, two-step labeled hormone back titration methods are less subject to artifacts due to abnormal binding proteins, changes in albumin, TBG, or increases in free fatty acids than are one-step hormone analogue methods.[31] [32] [33] . Thus, the clinician must be wary if the free T4 result by any method does not agree with the clinical state and the TSH. In such cases, another method should be used to estimate the free T4, such as quantitation of T4 in a dialysate or ultrafiltrate, the free T4 index should be measured, or the result should be ignored. For pregnant or severely ill

patients, the automated methods typically give falsely low results, particularly if these are performed using one-step procedures. A reasonable alternative for pregnancy is to use the normal range for the serum T4 concentration multiplied by 1.5 in lieu of an automated free T4 assay.

The Free T4Index (FT4I)

Particularly useful in estimating the free T4 in severely ill patients is the determination of the thyroid hormone–binding ratio (THBR), multiplying this result by the total T4 (or T3) to obtain a free hormone index (FT4I or FT3I). In this test, a tracer quantity of labeled T4 (or T3) is added to serum, which is then exposed to a solid phase matrix coated with T4 or T3 antibody or to an inert matrix that binds the iodothyronine irreversibly. The proportion of labeled T4 or T3 bound by the solid phase is then quantitated. This value, like the free fraction of T4 quantitated directly in a dialysate, varies inversely with the concentration of unoccupied TBG sites in the serum. Where tracer T3 is used, its binding to TBG is determined by the ratio of T4, not T3, to TBG in that T4 is present in 50- to 60-fold higher concentrations than T3, has a much higher affinity for TBG than does T3 and, therefore, determines the ratio of unoccupied to occupied TBG. The results of such assays are normalized by comparing them with those obtained simultaneously for standard control sera with normal TBG and serum T4

concentrations. This is generally done by dividing the result for the unknown sample by that obtained for control sera in the same assay. The quotient is the THBR, which typically has a normal range of 0.85 to 1.10. Because the THBR is proportional to the free fraction of the endogenous thyroid hormones in the serum, it can be multiplied by the total T4 (or T3) concentration to estimate the free thyroid hormone concentration, termed the free T3 or free T4 index (FT3I or FT4I) Because the normal THBR is 1.0, the FT4I has a normal range in units that is identical to that of the total T4 (or T3), for example, 64 to 142 for SI units and 5 to 11 in gravimetric terms.

Causes of a Suppressed TSH

The excess supply of thyroid hormone due to excessive exogenous thyroid hormone or increased endogenous thyroid hormone production is the most common cause of a reduction in the serum TSH. Patients Who present with clinical symptoms usually have concentrations of TSH in serum below 0.1 mU/L. Such patient's serum have increased free T4. In rare patients with low iodine intake, with clinical thyrotoxicosis, the FT4I is only high-normal despite a suppressed TSH. An FT3I is required in those patients to establish a diagnosis of T3 thyrotoxicosis. When thyroid hormone supply is only slightly in excess of the requirement for that patient, serum TSH is suppressed, but clinical manifestations are subtle or absent and the FT4I (and FT3I) are in the high-normal range. Such

minimal changes can occur with “euthyroid” Graves' disease, autonomous thyroid hormone-producing adenomas, multinodular goiters, subacute or painless thyroiditis, and the ingestion of an amount of exogenous thyroid hormone slightly greater than that required for metabolic needs. This condition is termed subclinical hyperthyroidism. After there is complete resolution of status of throtoxicosis there will be suppression of the hypothalamic-pituitary axis for a period of 3 months [34] [35]. The best test for assessing the physiologic state in such patients is the free T4 or FT4I. Because hCG can activate the TSH receptor, conditions in which hCG is elevated, such as in the first trimester of pregnancy, with twin pregnancies, during severe hyperemesis gravidarum, and in patients with hydatidiform mole or choriocarcinoma, the TSH concentration is often suppressed. TSH returns to normal in the second and third trimesters in the euthyroid patient. A persistently suppressed TSH (<0.1 mU/L) in the pregnant patient after the first trimester suggests that the hyperthyroidism is due to autonomous thyroid function.

Causes of an Elevated TSH

Usually in cases with an elevated TSH there will be a reduction T4 or T3 supply. The most usual explanation is primary hypothyroidism. Also there is elevated TSH in patients who are acutely ill like in renal insufficiency or the asynchrony in the return of the thyroid and the hypothalamic-pituitary axes to normal as these critically ill recover. The commonest aetiology for an elevated TSH worldwide is

iodine deficiency. Patients with dysfunction of hypothalamic-pituitary axes have low, normal, or increased serum TSH but they may have chemical and clinical Hypothyroidism because the biologic effectiveness of the circulating TSH is impaired due to abnormal glycosylation secondary to reduced TRH stimulation of the thyrotrophs. With replacement of glucocorticoid TSH returns to normalcy inspite of being previously elevated in cases of adrenal insufficiency. Despite the utility and general efficacy of the serum TSH measurement alone as a screening tool for identifying patients with thyroid dysfunction, a patient should not receive treatment for this dysfunction solely on the basis of an abnormal TSH. The TSH assay is an indirect reflection of thyroid hormone supply and does not, by itself, permit a conclusive diagnosis of a specific disorder of thyroid hormone production. Accordingly, the TSH abnormality must be verified and an alteration in thyroid hormone concentrations verified before initiating treatment.

Tests That Assess the Metabolic Impact of Thyroid Hormones

Basal Metabolic Rate

Thyroid hormones increase energy expenditure and heat production, as manifested by weight loss, increased caloric requirement, and heat intolerance. The normal values when adjusted for gender and age is from -15% to +5% . In patients who are severely hypothyroid it can be -40%, while in thyrotoxic patients it can be +25% to +50%. Abnormal, usually elevated, values are seen during recovery in burn

patients and in systemic disorders, such as febrile illnesses, pheochromocytoma, myeloproliferative disorders, anxiety, and disorders associated with involuntary muscular activity. Resting energy expenditure correlates very well with the free T4 and TSH in hypothyroid patients given varying doses of exogenous levothyroxine.

Biochemical Markers of Altered Thyroid Status

Occasionally lowdensity lipoprotein (LDL) cholesterol or markedly raised creatine kinase MM isoenzyme can be seen in hypothyroidism. These tests are not useful in the diagnosis of thyroid disease, but some, such as sex hormone–binding globulin (SHBG), ferritin, or LDL cholesterol, have been used as end-points in clinical studies of the responsivity of the liver to thyroid hormone in patients with thyroid hormone resistance.

Serum Thyroglobulin

The sensitivity of modern thyroglobulin (Tg) assays is 1 ng/mL or even less. The results can be artifactually altered by serum anti-Tg antibodies, and serum should be screened for Tg antibodies with a sensitive Tg-antibody immunoassay or for interferences with a recovery test. In immunoradiometric assays, interferences lead to underestimations of Tg or false-negative values with radioimmunoassays relatively unaffected especially if the antibody titer is low. Mean normal values usually vary with the type of assay used but they are in the range of 30 pmol/L (20 ng/mL). Concentrations are somewhat higher in women than in men and are

several fold elevated in pregnant women and in the newborn. Levels are elevated in three types of thyroid disorders: goiter and thyroid hyper function, inflammatory or physical injury to the thyroid, and differentiated follicular cell derived thyroid tumors. Transient elevations occur in patients with subacute thyroiditis and as a result of trauma to the gland during thyroid surgery or after I131 therapy. Subnormal or undetectable concentrations are found in patients with thyrotoxicosis factitia and aid in differentiating this disorder from other causes of thyrotoxicosis with a low thyroid radioiodine uptake (RAIU). Antithyroglobulin antibodies interfere with measurements of the Tg concentration precluding its use in patients with Hashimoto's disease. A major clinical value of measuring the level of serum Tg is in the management, but not in the diagnosis, of differentiated thyroid carcinoma. Serum Tg concentrations are increased in patients with both benign and differentiated malignant follicular-cell derived tumors of the thyroid and do not serve to distinguish between the two. After total thyroid ablation for papillary or follicular thyroid carcinoma, Tg should not be detectable, and its subsequent appearance signifies the presence of persistent or recurrent disease. Secretion of Tg is TSH-dependent. In the hypothyroid newborn, serum Tg is undetectable in patients with thyroid agenesis and is usually elevated in those with ectopic thyroid tissue or goiter.

Tests for Thyroid Autoantibodies

Autoantibodies to Thyroid Peroxidase and Thyroglobulin

Modern assay techniques for thyroid autoantibodies have good precision because they depend on the direct measurement of the interaction between autoantibody and autoantigen (i.e., the interaction between labelled thyroid antigen and the patient's serum). In general, the more sensitive an assay, the more precise and antigen-specific it is. However, many euthyroid individuals in our population exhibit low levels of autoantibodies and, therefore, the specificity of the more sensitive tests is reduced and the absolute concentration becomes more important; the higher the concentration of autoantibody, the greater the clinical specificityAntibodies to thyroglobulin (Tg) and thyroid peroxidase (TPO) are found in almost 100 % of patients with Hashimoto's disease which is otherwise called autoimmune thyroiditis and in 50% to 90% of cases of grave’s disease. Antibodies directed against the TSH receptor is also found in grave’s disease. Although the presence of such autoantibodies favors a diagnosis of an autoimmune cause for the hyperthyroidism over other causes, the tests are neither sensitive nor specific in this setting and are interpretable only as part of the clinical scenario. TSH receptor antibodies remain the test of choice in such patients.

Thyroid Autoantibodies in Nonautoimmune Thyroid Disorders

Persons with isolated thyroid nodules and cancer, multinodular goiter, sporadic goiter and insulin-dependent diabetes mellitus (IDDM) also have antibodies to Tg and TPO.

Radioiodine Uptake

The only direct test of thyroid function employs a radioactive isotope of iodine as a tag for the body's stable form of iodine, I 127. Measurements of RAIU are usually done at 24 hours. It indicates the rate at which thyroid hormone is synthesized and the rate at which it is released into the blood.

The perchlorate discharge test

In normal individuals, more than 90% of thyroidal radioiodine is present as iodotyrosine and iodothyronine within minutes of its entry into the thyroid. It is then no longer in the intracellular iodide pool. In patients with Pendred's syndrome or with other disorders that inhibit the iodination of tyrosine, such as Hashimoto's thyroiditis, or those receiving thiourea drugs, this process is delayed, as shown by the exit (discharge) of more than 10% of the thyroidal radioiodine within 2 hours of administration of 500 mg of KClO4. Perchlorate inhibits NIS function by competing with iodide for NIS, eliminating the iodide gradient that is required for maintaining the radioiodide in the gland. This illustrates that both iodide transport

by NIS at the basal pole of the thyrocyte and its efflux across the apical membrane by pendrin are required for thyroid hormone synthesis.

States Associated with Increased RAIU

Hyperthyroidism

Hyperthyroidism causes increased RAIU unless body iodide stores are increased. Such increases in uptake are always evident except in patients with severe thyrotoxicosis, in whom release of hormone can be so rapid that the thyroid content of I* has decreased to the normal range by the time the measurement is made. This condition is rare and is usually associated with obvious thyrotoxicosis.

Aberrant hormone synthesis

RAIU can be increased in the absence of hyperthyroidism in disorders in which iodine accumulation is normal but the secretion of hormone is impaired, such as in patients with abnormal thyroglobulin synthesis.The magnitude of the increase in uptake and the time at which the plateau is achieved vary with the nature and severity of the disorder. Differentiation of the foregoing states from hyperthyroidism is generally not difficult, because in the former, clinical findings and laboratory evidence of hyperthyroidism are lacking, and indeed hypothyroidism may be present.

Iodine deficiency

RAIU is increased in acute or chronic iodine deficiency, as demonstrated by measurement of urinary iodine excretion, with urinary iodine values lower than 100 μg/day, indicating deficiency. Chronic iodine deficiency is usually the result of an inadequate content of iodine in the food and water (endemic iodine deficiency). Patients with cardiac, renal, or hepatic disease may develop iodine deficiency if given diets severely restricted in salt, especially if diuretic agents are administered.

Response to thyroid hormone depletion

Rebound increases in RAIU are seen after withdrawal of antithyroid therapy, after subsidence of transient or subacute thyroiditis, and after recovery from prolonged suppression of thyroid function by exogenous hormone. A striking increase in uptake occurs in patients with iodide-induced myxedema after cessation of iodide administration. The duration of the rebound depends on the time required to replenish thyroid hormone stores.

Excessive hormone loses

In nephrotic syndrome, excessive losses of hormone in the urine occurring in association with urinary loss of binding protein cause a compensatory increase in hormone synthesis and RAIU. A similar sequence may occur when losses of hormone via the gastrointestinal tract are abnormal, as in chronic diarrheal states or

during ingestion of agents, such as soybean protein and cholestyramine, that bind T4 in the gut.

States Associated with Decreased RAIU

Exogenous thyroid hormone : Thyrotoxicosis factitia

Except in disorders in which homeostatic control is disrupted or overridden (e.g., Graves' disease or autonomously functioning thyroid nodules), administration of exogenous thyroid hormone suppresses TSH secretion and reduces the RAIU, usually to values below 5%. Low values of the RAIU in a patient who is clinically thyrotoxic may also indicate the presence of Thyrotoxicosis factitia, the syndrome produced by the ingestion of excess thyroid hormone. The unmeasurably low level of Tg in serum differentiates thyrotoxicosis factitia from other causes of thyrotoxicosis with decreased RAIU.

Disorders of thyroid hormone storage

The RAIU is usually low in the early phase of subacute thyroiditis and in chronic thyroiditis with transient hyperthyroidism. Here, inflammatory follicular disruption leads to loss of the normal storage function of the gland and leakage of hormone into the blood. In the early stage of subacute thyroiditis, leakage of hormone is usually sufficient to suppress TSH secretion and the RAIU. Transient hypothyroidism often occurs late in both diseases, when stores of preformed

hormone are depleted; the RAIU may return to normal or increased values at that time.

Exposure to excessive iodine

Common offenders are organic iodinated dyes used as x-ray contrast media and amiodarone. The duration of suppression of the uptake varies among individuals and with the compound administered. In general, dyes used for pyelography or CT scanning are cleared within a few months, whereas amiodarone may influence the uptake for up to 12 months due to its storage in fat. A single large dose of inorganic iodide can decrease uptake for several days, and chronic ingestion of iodide may depress the uptake for many weeks. Excessive quantities of iodine may also be present in vitamin and mineral preparations, vaginal or rectal suppositories, and iodinated antiseptics such as povidone. The measurement of urinary iodine excretion is an invaluable means of establishing or excluding the existence of excessive body iodide stores; the 24-hour iodine excretion can be extrapolated from the iodide-to-creatinine ratio in a random urine sample. Values in excess of 2 mg/day can account for a low RAIU value.

Thyroid Ultrasound

Ultrasonography is used increasingly to assist in the diagnosis of nodular thyroid disease, a reflection of the limitations of the physical examination and improvements in ultrasound technology. Using 10-MHz instruments, spatial

resolution and image quality are excellent, allowing the detection of nodules and cysts >3 mm. In addition to detecting thyroid nodules, ultrasound is useful for monitoring nodule size and for the aspiration of nodules or cystic lesions. Ultrasound-guided FNA biopsy of thyroid lesions lowers the rate of inadequate sampling. Ultrasonography is also used in the evaluation of recurrent thyroid cancer, including possible spread to cervical lymph nodes.

HYPOTHYROIDISM[26]

CAUSES OF HYPOTHYROIDISM

Primary

Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer

Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, *p*-aminosalicylic acid, interferon- and other cytokines, aminoglutethimide, sunitinib

Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation

Iodine deficiency

Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis

Overexpression of type 3 deoiodinase in infantile hemangioma

Transient

Silent thyroiditis, including postpartum thyroiditis

Subacute thyroiditis

Withdrawal of thyroxine treatment in individuals with an intact thyroid

After ^{131}I treatment or subtotal thyroidectomy for Graves' disease

Secondary

Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies

Isolated TSH deficiency or inactivity

Bexarotene treatment

Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Congenital Hypothyroidism

PREVALANCE

Hypothyroidism occurs in about 1 in 4000 newborns. It may be transient, especially if the mother has TSH-R blocking antibodies or has received antithyroid drugs, but permanent hypothyroidism occurs in the majority. Neonatal hypothyroidism is due to thyroid gland dysgenesis in 80–85%, to inborn errors of thyroid hormone synthesis in 10–15%, and is TSH-R antibody-mediated in 5% of affected newborns. The developmental abnormalities are twice as common in girls. Mutations that cause congenital hypothyroidism are being increasingly identified, but the vast majority remain idiopathic.

CLINICAL MANIFESTATIONS

The baby presents with features such an increased duration of jaundice, do not feed properly, reduction in tone of muscles, big tongue, also the presence of hernias of umbilicus. Symptoms include tiredness, weakness, dry skin, feeling cold, hair loss, difficulty concentrating and poor memory, constipation, weight gain with poor appetite, dyspnea, hoarse voice, menorrhagia (later oligomenorrhea or amenorrhea), paresthesia, impaired hearing. Signs include dry coarse skin; cool peripheral extremities, puffy face, hands, and feet (myxedema), diffuse alopecia,

bradycardia, peripheral edema, delayed tendon reflex relaxation, carpal tunnel syndrome, serous cavity effusions.

DIAGNOSIS AND TREATMENT

Because of the severe neurologic consequences of untreated congenital hypothyroidism, neonatal screening programs have been established. Diagnosis based on measurement of TSH or T4 levels in heel-prick blood specimens. When the diagnosis is confirmed, T_4 is instituted at a dose of 10–15 g/kg per day, and the dose is adjusted by close monitoring of TSH levels. T_4 requirements are relatively great during the first year of life, and a high circulating T_4 level is usually needed to normalize TSH. Early treatment with T_4 results in normal IQ levels, but subtle neurodevelopmental abnormalities may occur in those with the most severe hypothyroidism at diagnosis or when treatment is delayed or suboptimal.

Autoimmune Hypothyroidism

CLASSIFICATION

Hashimoto's or goitrous thyroiditis, atrophic thyroiditis. In this disease there will be a period in which increase in thyroid stimulating hormone maintains a normal quantity of T3 and T4. Though some may have minor symptoms, this state is said as subclinical hypothyroidism. Further in the course the quantity of free T4 becomes less while that of thyroid stimulating hormone increases still more and the

patient starts having more symptoms related to thyroid hormone deficiency (mostly thyroid stimulating hormone greater than 10 mIU/ litre). This is called to be clinical hypothyroidism.

PREVALANCE

The mean annual incidence rate of autoimmune hypothyroidism is up to 4 per 1000 women and 1 per 1000 men. It is more prevalent among some people in countries like japan, probably due to reasons related to genetics and increased long term consumption of foods rich in iodine. The mean age at diagnosis is 60 years, and there is an increase in prevalence of cases of clinical hypothyroidism as the age advances. Subclinical hypothyroidism is found in 6–8% of women (10% over the age of 60) and 3% of men. The annual risk of developing clinical hypothyroidism is about 4% when subclinical hypothyroidism is associated with positive TPO antibodies.

PATHOGENESIS

In Hashimoto's, it is characterized by an increased invasion of the gland by lymphocytes and also there will be presence of germinal center, the follicles decrease in size, metaplasia of oxyphil cells, will be no colloid, and presence of fibrosis of the gland. The disease like atrophic thyroiditis is characterized by still more increased increased fibrosis while the invasion by the lymphocyte cells is not

much as seen in case of hashimoto's , also the follicles present in the gland are decreased to almost total absence. This disease probably denotes the hashimoto's in it's last stage instead of a separate disease. Subjects are more prone to this disease called autoimmune hypothyroidism characterized by many kinds of factors relating to genes, environment, and in siblings they are more prone to develop grave's disease which is also known as autoimmune hypothyroidism. Human leukocyte antigen- DR polymorphisms like of DR 3,4,5 are seen among Europeans. There is a gene which plays a role in the regulation of T lymphocyte called CTLA-4 which has got polymorphisms in it. These two associations seen among the genes are also seen in other diseases caused by autoimmunity which teaches us the link seen with autoimmune hypothyroidism to diseases related to autoimmunity such as type one diabetes, disease of adrenals like addison's, anemia of the pernicious type and other diseases of the skin like vitiligo. The above two autoimmune mechanisms discussed are the reason for nearly 50% of the factors related to genes in a case of autoimmune hypothyroidism. Similar other genetic loci are yet to be found out. Down syndrome is linked with the above disease , autoimmune hypothyroidism because one of the gene present on chromosome twenty one plays a role in it. The effect caused by the sex steroid on the way in which the immunity of the person responds is probably the reason why the autoimmunity of the gland is seen more among women however one of the factors

in regards to the genes which is in fact associated with the chromosome X, the reason why lot of cases of autoimmune hypothyroidism is encountered in diseases like the turner's. The factors related to the environment which play a role in the development of the disease are not known much at this point of time. An increased consumption of iodine may play a role in the development of the disease we are discussing that is autoimmune hypothyroidism due to direct toxic effects on the gland or by other mechanisms related to immune response. With regards to infectious cause for autoimmune hypothyroidism we have not got much evidence except rubella syndrome which is acquired congenitally. The thyroiditis caused by infectious cause like virus do not play a role in the manifestation of the disease in discussion autoimmune hypothyroidism. The thyroid lymphocytic infiltrate in autoimmune hypothyroidism is composed of cells such as CD4+ and also cells like CD8+ which are in the activated state while also having B lymphocytes. The cells in the thyroid gland gets destroyed by cells like the CD8+, which destroy their targets by either perforin-induced cell necrosis or granzyme B–induced apoptosis. In addition, local T cell production of cytokines, such as tumor necrosis factor (TNF), IL-1, and interferon (IFN-gamma), may render thyroid cells more susceptible to apoptosis mediated by death receptors, such as Fas, which are activated by their respective ligands on T cells. The functioning of the cells of the thyroid gland are impaired by the action of the above cytokines and the cytokines

increase the molecules which induce inflammation through their increased expression by the cells of the thyroid gland and these molecules are other cytokines, human leukocyte antigen class one and two molecules, nitric oxide. Administration of high concentrations of cytokines for therapeutic purposes (especially IFN-gamma) is associated with increased autoimmune thyroid disease, possibly through mechanisms similar to those in sporadic disease. Antibodies to TPO and Tg are clinically useful markers of thyroid autoimmunity, but any pathogenic effect is restricted to a secondary role in amplifying an ongoing autoimmune response. TPO antibodies fix complement, and complement membrane-attack complexes are present in the thyroid in autoimmune hypothyroidism. However, the journey of thyroglobulin or the thyroid peroxidase antibodies through the placenta does not have any effect on the thyroid gland of the fetus which gives a clue that injury due to T lymphocyte cell is needed to destroy the gland. Up to 20% of patients with autoimmune hypothyroidism have antibodies against the TSH-R, which, in contrast to TSI, do not stimulate the receptor but prevent the binding of TSH. These TSH-R-blocking antibodies, therefore, cause hypothyroidism and, especially in Asian patients, thyroid atrophy. Their transplacental passage may induce transient neonatal hypothyroidism. Rarely, patients have a mixture of TSI and TSH-R-blocking antibodies, and the function of the gland fluctuates between hyper functioning and hypo functioning depending

upon which antibody plays a major role at that moment. It is very tough to say in which route the disease will progress in those people and need a close watch on the functioning of the gland. Various bioassays are in vogue to say that TSH-R-blocking antibodies reduce the cyclic AMP–inducing effect of TSH on cultured TSH-R-expressing cells, but these assays are difficult to perform. Assays like TBII which quantify how much antibodies bind with the receptor by competing with radio labeled thyroid stimulating hormone cannot separate TSI- and TSH-R-blocking antibodies, but if the outcome is positive in the subject it points out that blocking antibodies exist. These assays does not generally alter clinical management, although it may be useful to confirm the cause of transient neonatal hypothyroidism.

CLINICAL MANIFESTATIONS

Patients with Hashimoto's thyroiditis may present because of goiter rather than symptoms of hypothyroidism. Patients with atrophic thyroiditis or the late stage of Hashimoto's thyroiditis present with symptoms and signs of hypothyroidism. The skin is dry, and there is decreased sweating, thinning of the epidermis, and hyperkeratosis of the stratum corneum. skin thickening without pitting (myxedema). Typical features include a puffy face with edematous eyelids and nonpitting pretibial edema. There is pallor, often with a yellow tinge to the skin.

Nail growth is retarded, and hair is dry, brittle, difficult to manage, and falls out easily and there is thinning of the outer third of the eyebrows, although this is not a specific sign of hypothyroidism. Other common features include constipation and weight gain (despite a poor appetite). Libido is decreased in both sexes, and there may be oligomenorrhea or amenorrhea in long-standing disease, but menorrhagia is also common. Fertility is reduced, and the incidence of miscarriage is increased and galactorrhea. Myocardial contractility and pulse rate are reduced, leading to a reduced stroke volume and bradycardia. Increased peripheral resistance may be accompanied by hypertension, particularly diastolic and there is cool extremities. Pericardial effusions, conductive deafness, dyspnea may be caused by pleural effusion, impaired respiratory muscle function, diminished ventilatory drive, or sleep apnea. Carpal tunnel and other entrapment syndromes are common, as is impairment of muscle function with stiffness, cramps, and pain. On examination, there may be slow relaxation of tendon reflexes and pseudomyotonia. Memory and concentration are impaired. Experimentally, PET scans examining glucose metabolism in hypothyroid subjects show lower regional activity in the amygdala, hippocampus, and perigenual anterior cingulated cortex, among other regions, and this activity corrects after thyroxine replacement. Rare neurologic problems include reversible cerebellar ataxia, dementia, psychosis, and myxedema coma. Hashimoto’s encephalopathy has been defined as a steroid-responsive syndrome

associated with TPO antibodies, myoclonus, and slow-wave activity on electroencephalography, but the relationship with thyroid autoimmunity or hypothyroidism is not established. The hoarse voice and occasionally clumsy speech of hypothyroidism reflect fluid accumulation in the vocal cords and tongue. The features described above are the consequence of thyroid hormone deficiency. However, autoimmune hypothyroidism may be associated with signs or symptoms of other autoimmune diseases, particularly vitiligo, pernicious anemia, Addison's disease, alopecia areata, and type 1 diabetes mellitus. Less-common associations include celiac disease, dermatitis herpetiformis, chronic active hepatitis, rheumatoid arthritis, systemic lupus erythematosus (SLE), myasthenia gravis, and Sjögren's syndrome. Thyroid-associated ophthalmopathy, occurs in about 5% of patients with autoimmune hypothyroidism. Autoimmune hypothyroidism is uncommon in children and usually presents with slow growth and delayed facial maturation. The appearance of permanent teeth is also delayed. Myopathy, with muscle swelling, is more common in children than in adults. In most cases, puberty is delayed, but precocious puberty sometimes occurs. There may be intellectual impairment if the onset is before 3 years and the hormone deficiency is severe.

LABORATORY EVALUATION

A normal TSH level excludes primary (but not secondary) hypothyroidism. If the TSH is elevated, an unbound T4 level is needed to confirm the presence of clinical

hypothyroidism. Once subclinical hypothyroidism otherwise the existence of clinically manifested hypothyroidism is found out the cause for the disease is found out by showing the existence of antibodies to the thyroid perroxidase, which are present in >90% of patients with autoimmune hypothyroidism. If the reason for the aetiology of the existence of the goiter when present along with hypothyroidism, fine needle aspiration biopsy clinches the diagnosis that is autoimmune thyroiditis. Also there will be some changes seen in hypothyroidism such as more creatine phosphokinase, hypercholesterolemia, hypertriglyceridemia, and decreased haemoglobin presenting as anemia.

Treatment: Hypothyroidism

If there is no residual thyroid function, the daily replacement dose of levothyroxine is usually 1.6 μg/kg body weight (typically 100–150 μg). In many patients, however, lower doses suffice until residual thyroid tissue is destroyed. In patients who develop hypothyroidism after the treatment of Graves' disease, there is often underlying autonomous function, necessitating lower replacement doses (typically 75–125 μ g/d). Adult patients under 60 without evidence of heart disease may be started on 50–100 μ g levothyroxine (T4) daily. The dose is adjusted on the basis of TSH levels, with the goal of treatment being a normal TSH, ideally in the lower half of the reference range. TSH responses are gradual and should be measured

about two months after beginning treatment otherwise when there is any alteration made to the dose in which the hormone is given. The clinical effects of levothyroxine replacement are slow to appear. Patients may not experience full relief from symptoms until 3–6 months after normal TSH levels are restored. The dose of the hormone is adjusted by increasing about 12.5 or 25 microgram if the thyroid stimulating hormone is having high values and decreases in dosage should be made in the same quantity if the thyroid stimulating hormone is having low values. Subjects with a less value of thyroid stimulating hormone due to any aetiology which includes overtreatment with the hormone are prone to develop cardiac problems like atrial fibrillation, decreased density of the bone. Although dessicated animal thyroid preparations (thyroid extract USP) are available, they are not recommended because the ratio of T_3 to T4 is nonphysiologic. The use of levothyroxine combined with liothyronine (triiodothyronine, T_3) has been investigated, but benefit has not been confirmed in prospective studies. There is no place for liothyronine alone as long-term replacement, because the short half-life necessitates three or four daily doses and is associated with fluctuating T_3 levels. Once full replacement is achieved and TSH levels are stable, follow-up measurement of TSH is recommended at annual intervals and may be extended to every 2–3 years if a normal TSH is maintained over several years. It is important to ensure ongoing adherence, however, as patients do not feel any symptomatic

difference after missing a few doses of levothyroxine, and this sometimes leads to self-discontinuation. In patients of normal body weight who are taking 200 μ g of levothyroxine per day, an elevated TSH level is often a sign of poor adherence to treatment. This is also the likely explanation for fluctuating TSH levels, despite a constant levothyroxine dosage. Such patients often have normal or high unbound T4 levels, despite an elevated TSH, because they remember to take medication for a few days before testing; this is sufficient to normalize T_4, but not TSH levels. It is important to consider variable adherence, because this pattern of thyroid function tests is otherwise suggestive of disorders associated with inappropriate TSH secretion. Because T_4 has a long half-life (7 days), patients who miss a dose can be advised to take two doses of the skipped tablets at once. Other causes of increased levothyroxine requirements must be excluded, particularly malabsorption (e.g., celiac disease, small-bowel surgery), estrogen therapy, and drugs that interfere with T_4 absorption or clearance such as cholestyramine, ferrous sulfate, calcium supplements, lovastatin, aluminum hydroxide, rifampicin, amiodarone, carbamazepine, and phenytoin. For subclinical hypothyroidism the most recent guidelines do not recommend treatment if TSH levels are below 10 mIU/L. It is important to confirm any elevation of TSH is sustained for 3 months before treatment is given.

SPECIAL TREATMENT CONSIDERATIONS

Rarely, levothyroxine replacement is associated with pseudotumor cerebri in children. Presentation appears to be idiosyncratic and occurs months after treatment has begun. Women with a history or high risk of hypothyroidism should ensure that they are euthyroid prior to conception and during early pregnancy as maternal hypothyroidism may adversely affect fetal neural development and cause preterm delivery. The presence of thyroid autoantibodies alone, in a euthyroid patient, is also associated with preterm delivery, and outcome may be improved by levothyroxine treatment. Thyroid function should be evaluated immediately after pregnancy is confirmed and at the beginning of the second and third trimesters. The dose of levothyroxine may need to be increased by 50% during pregnancy and returned to previous levels after delivery. Elderly patients may require 20% less thyroxine than younger patients. In the elderly, especially patients with known coronary artery disease, the starting dose of levothyroxine is 12.5–25 μg/d with similar increments every 2–3 months until TSH is normalized. In some patients, it may be impossible to achieve full replacement despite optimal antianginal treatment. Emergency surgery is generally safe in patients with untreated hypothyroidism, although routine surgery in a hypothyroid patient should be deferred until euthyroidism is achieved. Myxedema coma still has a high mortality rate, despite intensive treatment. Clinical manifestations include reduced level of

consciousness, sometimes associated with seizures, as well as the other features of hypothyroidism. Hypothermia can reach 23°C (74°F). There may be a history of treated hypothyroidism with poor compliance, or the patient may be previously undiagnosed. Myxedema coma almost always occurs in the elderly and is usually precipitated by factors that impair respiration, such as drugs (especially sedatives, anesthetics, antidepressants), pneumonia, congestive heart failure, myocardial infarction, gastrointestinal bleeding, or cerebrovascular accidents. Sepsis should also be suspected. Exposure to cold may also be a risk factor. Hypoventilation, leading to hypoxia and hypercapnia, plays a major role in pathogenesis; hypoglycemia and dilutional hyponatremia also contribute to the development of myxedema coma. Levothyroxine can initially be administered as a single IV bolus of 500 μg, which serves as a loading dose. Although further levothyroxine is not strictly necessary for several days, it is usually continued at a dose of 50–100 μg/d. If suitable IV preparation is not available, the same initial dose of levothyroxine can be given by nasogastric tube (though absorption may be impaired in myxedema). An alternative is to give liothyronine (T_3) intravenously or via nasogastric tube, in doses ranging from 10 to 25 μg every 8–12 h. Another option is to combine levothyroxine (200 μg) and liothyronine (25 μg) as a single, initial IV bolus followed by daily treatment with levothyroxine (50–100 μg/d) and liothyronine (10 μg every 8 h). External warming is indicated only if the

temperature is <30°C. Parenteral hydrocortisone (50 mg every 6 h) should be administered. Any precipitating factors should be treated, including the early use of broad-spectrum antibiotics, pending the exclusion of infection. Ventilatory support with regular blood gas analysis is usually needed during the first 48 hours. Hypertonic saline or IV glucose may be needed if there is severe hyponatremia or hypoglycemia. Hypotonic IV fluids should be avoided because they may exacerbate water retention secondary to reduced renal perfusion and inappropriate vasopressin secretion. The metabolism of most medications is impaired, and Sedatives should be avoided if possible or used in reduced doses. Medication blood levels should be monitored, when available, to guide dosage.

SUBCLINICAL HYPOTHYROIDISM

The term subclinical hypothyroidism was originally used to describe the patient with a low-normal free T4 but a slightly elevated serum TSH level. Other terms for this condition are mild hypothyroidism early thyroid failure, preclinical hypothyroidism, and decreased thyroid reserve. The TSH elevation in such patients is modest, with values typically between 4 and 15 mU/L, although patients with a TSH above 10 mU/L more often have a reduced free T4 and may have some hypothyroid symptoms.

PREVALENCE AND NATURAL HISTORY

Hypothyroidism is much higher in females than males and more cases are seen as age advances. The overall prevalence has been reported to range from 4–10% in large general population screening surveys[36-40] and from 7–26% in studies of the elderly[36-38], [21,24,41-44]. Subclinical hypothyroidism is a condition which is usually seen in patients before they develop the full clinical picture with the classic symptoms of hypothyroidism thereby becoming patients with clinical hypothyroidism. It has been found out from some studies that about 3 to 18% of people who were diagnosed as subclinical hypothyroidism ultimately converted into patients of hypothyroidism with low free T3 and low free T4 with elevated TSH who were followed for a period of one year [43] [44], [45-50].There is evidence from a study conducted by some researchers regarding how subclinical hypothyroidism evolves naturally in about 154 women with the disease who were followed for a period of ten years and it was found out that about 57% with the disease still had it while 34% developed full blown hypothyroidism and 9% had their TSH values return to normalcy. The strongest predictors of progression are the following determinants like patients who had antibodies against the thyroid, the quantity of TSH more than twenty microunits per milliliter of serum, in the past had their thyroid shrunken with radioiodine in those with graves disease, radiation treatment for cancers not relating to thyroid and finally those on lithium treatment

[43-49]. One Prevalence Study [37] which was done in Colorado in which the researchers found out the TSH values in the serum and also recorded the symptoms experienced by about 25,000 people. In this study it was found out that 9.5% of them had TSH above the normal range and the interesting fact is that 8.9% of the people who turned out with their TSH above normal range did not receive any replacement with thyroid hormone; also the TSH value in 75% people was between five and ten micro units per milliliter of serum.

Effects on serum lipid levels

Several cross sectional studies show that serum cholesterol levels are elevated in individuals with mild thyroid failure when compared with euthyroid controls [38]. One of the studies done in Colorado pointed out the fact that total cholesterol's value of euthyroid subject's mean was two hundred and sixteen mg/dL and two hundred and twenty four mg/dL in subjects with SH[37]. Many studies done showed that there is a decrease in LDL cholesterol in those treated with levothyroxine. But the majority of these researches showing advantage of treatment is not for those subjects with thyroid stimulating hormone in the serum between five and ten mIU/L. It was shown in the meta analysis conducted with thirteen studies that the cholesterol levels showed an improvement with treatment[51]. But it was found out that in one of the reviews conducted in the year 2004 the data were not found to be enough to prove advantage of levothyroxine treatment with relation to the

cholesterol levels[40].This shows that the cholesterol values in the subject will decrease with hormone treatment if they have the thyroid stimulating hormone in the serum more than ten mIU/L and doubtful if the thyroid stimulating hormone value is below ten mIU/L.

CARDIAC EFFECTS

Studies have shown slowed left ventricular relaxation time, increased vascular tone at rest, and left ventricular systolic dysfunction with exercise and impaired endothelial function [52]. Some studies have shown improvement of cardiac contractibility and systolic time interval with levothyroxine therapy [52]. Rotterdam Study pointed out that subclinical hypothyroidism is linked to myocardial infarction also to another cardiac disease like the calcific disease of the aortic valve [24]. Also multiple meta analyses has been done about observational studies and researchers have found a link with subclinical hypothyroidism and ischemic heart disease[53-55].

SOMATIC AND NEUROMUSCULAR EFFECTS

Patients with subclinical hypothyroidism have symptoms like dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramps, cold intolerance, puffy eyes, constipation, and hoarseness. Findings like improper functioning of peripheral nerves characterized by reduced amplitude[56] and

reflexes like the stapedial having some problems [57] been found. Also problems like increase in the creatine phosphokinase[58] , activities like excess physical exertion causes a rise in lactate[59] , and furthermore findings like repeated discharges are seen in investigations like surface electromyography [60]

TREATMENT

Risk and benefits of treatment

There are studies which have evaluated the advantages of treatment of subclinical hypothyroidism and it has been found that treating the condition causes a favourable change in the lipid status, some symptoms associated with the disease are cleared and to add to the advantage it stalls the patient from ending up in gross hypothyroidism[3]. Quite a few researches have also found out some perks due to treatment like a decrease in the LDL and the total amount of cholesterol in those patients treated with l-T4 hormone [61,62]. But it has also been found out that treating aged patients with this hormone gives some problems like increase in the thyroid hormone levels in blood thereby causing cardiac problems fibrillation of the atrium and also bone weakening due to decrease in bone cells. However the benefits of improvement in the cholesterol levels is not seen in those subjects who presented with values of TSH below 10 mU/liter [61,63,64].

Subclinical hypothyroidism with serum thyroid stimulating hormone between 5.1 and 10 mU/L

There are no studies which have been done on a huge scale with randomization to show a definite bringing down of cholesterol due to levothyroxine treatment in this group of patients. One of the studies done in this subgroup of patients with thyroid stimulating hormone failed to bring out any reduction in cholesterol[65]. Therefore before starting treatment with levothyroxine in this subgroup doctors should first individualize the patient and many factors like pregnancy or intention of pregnancy, goiter, therapeutic trial for possible hypothyroid symptoms, patient preference, childhood and adolescence, 2 TSH levels >8 mIU/L, bipolar disorder, depression, infertility, presence of antithyroid antibodies, progressive TSH increase, ovulatory dysfunction, young age, hyperlipidemia?

Subclinical hypothyroidism with thyroid stimulating hormone in the serum above 10 mU/L

Most endocrinologists say that everyone with subclinical hypothyroidism and having thyroid stimulating hormone in the serum in excess of 10 mIU/L should commence their treatment with the hormone that is levothyroxine[66,67]. There is quite a few data showing the harmful effects of subclinical hypothyroidism in this

category of patients. Various studies depicted that hormone treatment have brought about an eight milligram decrease in LDL values[51,68].

Subclinical hypothyroidism during pregnancy

Woman who are pregnant and those planning to get pregnant presenting with subclinical hypothyroidism should be treated with levothyroxine so that TSH is brought again in the normal range. This is because high TSH causes increased fetal wastage or neuropsychological complications in the offspring. Although there are no published intervention trials assessing the benefits of thyroid hormone replacement in this special population, the potential benefit-risk ratio of levothyroxine therapy justifies its use. The dose of levothyroxine required during pregnancy increases and so the concentration of serum TSH should be seen every 6 to 8 weeks and the dose adjusted. The risks associated with the appropriate management of levothyroxine therapy are minimal.

Subclinical hypothyroidism in treated overt hypothyroid individuals

When subclinical hypothyroidism is noted in levothyroxine treated patients with overt hypothyroidism, the dosage of levothyroxine should be adjusted to bring serum TSH into reference range. Whether the target TSH level should be in the lower half of reference range is controversial because there are no data demonstrating improved clinical outcomes with this strategy. Nevertheless, when

serum TSH is in the upper half of reference range and levothyroxine treated patients continue to note symptoms suggestive of hypothyroidism, it is reasonable to increase levothyroxine dosage to bring serum TSH into lower portion of reference range. The rapidity of dosage adjustment depends on patient's age and medical co morbidities. Minimal TSH elevations may not require dosage adjustment in patients who feel well, particularly those with arrhythmias or other cardiac disorders.

THYROXINE THERAPY

The treatment with levothyroxine be given to all people with subclinical hypothyroidism and having thyroid stimulating hormone in the serum more than 10 mIU/L , also for people having thyroid stimulating hormone in the serum between 5.1 and 10 mIU/L the decision for treatment is done on an individual patient basis. Mostly treatment is started with minimal doses of levothyroxine in the range of 50 to 75 μg [69]. Since many patients ultimately land up in hypothyroidism few doctors prescribe a full dose weighing on the benefits of treatment. But it is recommended to begin the treatment for these patients with 25 to 75 μg daily taking in to consideration various factors like the subject's age, the quantity of free thyroxine and the quantity of serum thyroid stimulating hormone in the subject. After a period of eight weeks the level of thyroid stimulating hormone in the serum should be found out and there be adjustment made to the dosage. On getting a normal

thyroid stimulating hormone level in the serum the hormone level can be seen after a period of six months and after that once a year. In patients who are young the target for maintaining the level of thyroid stimulating hormone in the serum should be between 0.3 and 3 mIU/L. While for patients who are of elderly category the range can be placed higher. In an effort to reduce the TSH level in serum by prescribing the hormone we should also have an eye on the harmful effects of the therapy causing an over suppression of TSH and thereby affecting the patient. Subclinical hypothyroidism is seen when the patient has normal level of free thyroxine in the serum while having their thyroid stimulating hormone in the serum in excess of the normal value. It is advised to start treatment with levothyroxine if the patient has thyroid stimulating hormone in the serum more than 10 mIU/L even if he has got normal levels of free thyroxine in his serum. These patients clearly have benefits of treatment however for those patients presenting with values of thyroid stimulating hormone in the serum in the range of 5 to 10 mIU/L it is controversial. The points for starting treatment with levothyroxine are that subclinical hypothyroid patients frequently land up in hypothyroidism, there is a positive change in the quality of life and also this condition can affect the patient's heart in the long run thereby compromising on the life expectancy of the patient. However some recent data are showing that the risk to the heart is seen in subjects less than the age of seventy years; while those

patients who are between seventy to eighty years have not developing added risk and finally in those patients above the age of eighty years in fact have the luxury of protection to the heart due to the treatment. Having seen the pros and cons of treatment one grey area which needs to be addressed is in those patients who present with values of serum TSH below ten mIU/L and some multicentered randomised control studies are necessary to evaluate the efficacy of treating these patients with levothyroxine. But it does not mean that we should not treat these patients but the fact is that treatment should be based upon the individual patient with the treating physician taking a lot of factors like if the patient wants treatment, if he has got any symptoms or if he has got some co morbid conditions.

MATERIALS AND METHODS

Case selection

Women above 50 years of age attending Medical outpatient clinic of Chengalpattu medical college and hospital from January 2012 to june 2012 were studied. The sample consisted of a random selection of 100 women. Informed consent was obtained from all participants. All the participants were examined for thyroid function. Women with subclinical hypothyroidism (defined as TSH > 5.5μIU/ml with normal free T4 and free T3) were considered as cases, and women without subclinical hypothyroidism were considered as controls. Laboratory measurements and clinical assessment was carried out in all the participants.

Exclusion criteria

Those with

Chronic renal failure

Known thyroid disease

History of neck irradiation

Severe illness (such as recent myocardial infarctions, infections, severe heart failure or recent intensive care admission)

Taking drugs such as amiodarone, beta-blockers, interferon –α

were excluded

Measurements

All the patient were done Thyroid function test- Free T3, Free T4 and TSH levels. Thyroid function test is done using the electro chemiluminence method. The normal range for Free T3 it is 1.70-4.20 pg/ml, for Free T4 it is 0.70-1.80 ng/dl and for TSH is 0.30-5.50 μIU/ml.

Clinical Assessments

All the Participants were examined for symptoms related to hypothyroidism and also for the presence of goiter. Also general examination and clinical examination of cardiovascular, respiratory, abdominal and central nervous system were made.

Analytical methods

The following data were collected from all the participants

• Age

• Presence of Hypertension (defined as BP > 140/90 mm Hg on more than one occasion or the patient is known to be hypertensive)

• Diabetes mellitus (defined as fasting blood sugar > = 126 mg% on two consecutive readings one month apart or the patient is known to be diabetic)

• Ischemic heart disease (defined as angina or myocardial infarction by self report or by analysis of standard 12 lead ECG for ischemic heart disease changes or echocardiography)

• Comparison between cases (subclinical hypothyroidism) and normal control subjects of similar age and ethnic group was done with regard to presence of IHD, Hypertension and Diabetes mellitus

Statistical Analysis

Statistical analysis was done using the statistical package for social sciences (SPSS).Different statistical methods were used as appropriate. Mean ± SD was determined for quantitative data and frequency for categorical variables. The independent t- test was performed on all continuous variables. The normal distribution data was checked before any t-test. The Chi-Square test was used to analyze group difference for categorical variables. In logistic regression models, age was adjusted for estimation of each or all the independent effects of hypertension, ischemic heart disease and diabetes mellitus. A p- value < 0.05 was considered significant.

RESULTS

100 elderly women above 50 years of age who attended the medical outpatient clinic of Chengalpattu medical college and hospital during the period of study were studied and 21 women were found to have the criteria set for the definition of subclinical hypothyroidism which meant a rate of 21 %. Patients with subclinical hypothyroidism were regarded as cases and remaining 79 patients were the control group.

Differences were seen in the mean age distribution among cases and controls are shown in table 1 and fig 1

Table 1

Age in years	Patients with SH	Patients without SH
50-59	7	36
60-69	8	25
70 and above	6	18

Out of the 43 patients in 50-59 age group 7 (16.28%) of them had subclinical hypothyroidism. Out of the 33 patients in 60-69 age group 8 (24.24%) of them had subclinical hypothyroidism. Out of the 24 patients in 70 and above age group 6

(25%) of them had subclinical hypothyroidism. The mean TSH level in patients with subclinical hypothyroidism was 9.02 μIU/ml. For FT4 it was 0.90 ng/dl and for FT3 it was 1.83 pg/ml. Differences in FT4, FT3, TSH distribution were seen among cases and controls as shown in Table 2 and fig 2

Table 2

Mean	Patients with SH	Patients without TSH
FT3 (pg/ml)	1.83	2.30
FT4 (ng/dl)	0.90	1.12
TSH (μIU/ml)	9.02	2.13

There were 21 patients with TSH level more than 5.5 μIU/ml, the upper level of normal range (0.30-5.5 μIU/ml). They are the subclinical hypothyroid patients in this study. Of those 21 patients 14 (66.67%) had TSH level between 5.5 to 10 μIU/ml. The remaining 7 (33.33%) patients had TSH levels more than 10 μIU/ml as shown in the following Table 3 and fig 3

Table 3

TSH levels in patients with SH

TSH level in μIU/ml	No. of patients(%) Total no = 21
5.5 – 10	14 (66.67)
> 10	7 (33.33)

Symptoms of hypothyroidism were seen in 6 out of 21 (28.57%) patients with subclincal hypothyroidism. The most common complaints were fatigability and constipation, followed by weight gain. The frequency of hypothyroid symptoms in the subclinical hypothyroid patients are as shown in the table 4 and fig 4

Table 4

Frequency of hypothyroid symptoms in patients with SH

Fatigability	5 (23.81%)
Constipation	5 (23.81%)
Weight gain	3 (14.29%)
Goiter	2 (9.52%)
Others(cold intolerance, infertility etc)	2 (9.52%)

There was goiter present in 2 out of 21 patients with subclinical hypothyroidism (9.52%) and 5 out of 79 patients without subclinical hypothyroidism (6.3%). Other symptoms like cold intolerance infertility were present in 2 of the 21 patients (9.52%) with subclinical hypothyroidism and 1 of the 79 patients (1.2 %) without subclinical hypothyroidism. The incidence of risk factors like hypertension diabetes and ischemic heart disease were compared between patients with subclinical hypothyroidism and control. They were analyzed independently with chi-Square test. The p- value showed that patients with subclinical hypothyroidism were significantly associated with ischemic heart disease compared to controls. The p- value is not significant for hypertension and diabetes. This is shown in table 5 and fig 5

Table 5

	Patients with SH	Patients without SH	p- value
IHD	5 (23.81%)	4 (5.06%)	0.0185
DM	3 (14.29%)	17 (21.52%)	0.5545
HT	5 (23.81%)	22 (27.85%)	0.7892

DISCUSSION

Subclinical hypothyroidism has high prevalence among elderly women. The prevalence in elderly ranges from 7 – 26 % in various studies [36-38, 21,24,41-44] with the highest rate approaching 26% in elderly women [1,9,24,44]. Our study has a prevalence rate of 21 % which is in concordance with the other studies. Large number of surveys have shown that the percentage of cases with TSH < 10μIU/ml in cases of subclinical hypothyroidism is 55-85% [6,24,44,70,71]. 66.67% of our cases with subclinical hypothyroidism had TSH levels < 10μIU/ml. Many studies have shown that the thyroid antibody test on these patients with increased thyroid stimulating hormone turned out to be positive in the range of twenty to seventy eight percent[6,24,44,70,71]. Studies have shown that nearly 30% of the patients with subclinical hypothyroidism have symptoms of thyroid hormone deficiency [37,72]. Fatigability and weight gain were the most common symptoms [73], but not all studies have found his to be true [21]. In concordance with these studies our study demonstrated 28.57% of patients with subclinical hypothyroidism had symptoms of thyroid hormone deficiency of which fatigability (23.8%) and constipation (23.8%) were the most common. On support of the above findings researchers who conducted one study in Switzerland with a large number of women like above 300 subjects who had hypothyroidism found out that among 93 patients with subclinical hypothyroidism 24% of them presented with symptoms seen in

hypothyroidism [72]. These findings drive home the fact that it is not easy to diagnose a case of primary hypothyroidism by simply seeing the symptomatology profile alone. Furthermore people who presented with normal thyroid status and those with subclinical hypothyroidism cannot be easily found out only based on symptoms. Even though these studies showing some significant statistics in big number of people , when it comes to a single patient it is not easy to separate a person who presents with normal thyroid hormone levels from another person presenting with either hypothyroidism or subclinical hypothyroidism. There are five studies which have shown that there is improvement in psychological levels, symptoms associated with SH and also improvement in life quality[63,74-77]. Out of the above studies only two resulted in improvement[74,77], while the average thyroid stimulating hormone values were above 11 mU/L. One of the studies showed only a mild but significant benefit in the form of difference in the rate of response in the range of twenty four percent when compared with the placebo and those treated with thyroxine hormone, furthermore no factors could show who will gain from thyroid hormone therapy[63]. While there was no advantage of thyroid hormone therapy shown by the 2 studies which were remaining[75,76]. Out of these 2 studies one of them showed an improvement in the memory scores due to hormone therapy on comparison to placebo[75] while the other one but no other included patients with thyroid stimulating hormone between five to ten micro units per litre

showed some surprising outcomes. Only few symptoms relating to thyroid hormone deficiency were made out in the group which was treated with thyroid hormone and those treated with placebo[76]. Also patients who were in the range of 5-10 mU/L thyroid stimulating hormone were not sure if they are prescribed thyroid hormone therapy or placebo[76] . Combining the results above from the trials it can be taken that 1) patients with TSH between 5 to 10 mU/liter did not gain significantly from thyroid hormone therapy than the patients who were prescribed placebo, 2) out of those subjects presenting with worser subclinical hypothyroidism only twenty five percent of them gained from thyroxine hormone therapy 3) needless use of thyroid hormone therapy would only rarely improve symptoms associated with thyroid hormone deficiency on the fact that large number of people with SH have values of TSH between 5 to 10 mU/liter. Therefore in subjects presenting with thyroid stimulating hormone in the serum greater than ten 10 mU/liter, no debate is there and therapy is advised. This is reasonable because the conversion rate of these subjects into clinical hypothyroidism is more and LDL is decreased eight percentage with thyroxine treatment[78]. The treatment with thyroxine in these subjects with SH can provide good results with improvement of symptoms and also other systems. In subjects with thyroid stimulating hormone between five and ten mU/liter there is a provision for observation or therapy is started with regard to an individual patient.

The association between subclinical hypothyroidism and coronary heart disease is still somewhat controversial [24,54,79,80,81]. The Busselton Health Study reported that subclinical hypothyroidism is an independent risk factor for coronary heart disease [81]. Also, several studies have shown an association between subclinical hypothyroidism and either specific age ranges or TSH levels. The Rotterdam Study [24] showed a higher prevalence of atherosclerotic coronary vascular disease in female subclinical hypothyroidism patients who were 55 years of age or older. However, Ochs et al. [54] found in their metaanalysis using population-based cohort studies that the relative risk of subclinical hypothyroidism for coronary heart disease was significantly higher in subjects younger than 65 years, but not in subjects of age 65 years and older. Razvi et al. [82] also reported results from a meta-analysis showing that subclinical hypothyroidism is associated with increased coronary heart disease in subjects from younger populations only. The degree of subclinical hypothyroidism could be another important factor. subclinical hypothyroidism subjects with a TSH >=10 mU/l may also have an increased coronary heart disease risk, and recent data have shown that subclinical hypothyroidism is associated with an increased risk of coronary heart disease events and coronary heart disease mortality [54,83]. In addition, the Wickham survey, a large-scale, long term follow-up study, found no evidence to suggest that subclinical hypothyroidism is associated with an increased risk of ischemic heart

disease [23]. Our present study showed a significant increase in IHD in patients with subclinical hypothyroidism compared with controls (p value of 0.0185) . Several studies on association between subclinical hypothyroidism and dyslipidemia have been done. A study done by Althaus et al. [12] found out that the quantity of low density lipoprotein cholesterol was more while that for high density lipoprotein cholesterol was less in patients presenting with this condition when they were compared with people who were euthyroid, after the investigators adjusted for factors like age of the patient, body mass index and sex. This study[12] shows us the reason why patients with subclinical hypothyroidism end up having an increased incidence of affection of the heart in the form of coronary heart disease. One report[9] from Colorado in which the prevalence of diseases of the thyroid was studied pointed out that subjects presenting with subclinical hypothyroidism had an increase in total cholesterol and low density lipoprotein cholesterol which was significant when compared to euthyroid subjects but there was not much difference in the levels of triglycerides and high density lipoprotein cholesterol. These results were similar to other researchers Efstathiadou et al. [84] who also showed that subjects with subclinical hypothyroidism presented with increased quantity of total cholesterol and low density lipoprotein cholesterol but not much difference in the levels of triglycerides and high density cholesterol compared to euthyroid people. The quantity of lipid in a patient is decided by many things. It has been shown by

various study works that the hormones released by the thyroid play a role in changing the cholesterol levels in the patients. These hormones results in more production of cholesterol by inducing hydroxymethylglutaryl coenzyme A which is an important enzyme related to the production of cholesterol. There is a more production of low density lipoprotein cholesterol receptor because low density lipoprotein cholesterol receptor gene has a thyroid hormone responsive element which is acted upon by T3 to increase it's expression[85,86]. Subjects with hypothyroidism presented with more amount of total cholesterol, triglyceride and low density lipoprotein cholesterol while they had less high density lipoprotein cholesterol. This is due to the mechanism given above as said by the investigators in subclinical hypothyroidism. Patients with subclinical hypothyroidism did not differ from controls with regard to hypertension and diabetes in previous studies [87,72]. Our study also proves it true. In data from a cross-sectional study of 2,033 participants carried out by Walsh et al [88], who showed that mean systolic blood pressure, diastolic blood pressure and the prevalence of hypertension did not differ significantly between subclinical hypothyroidism and euthyroid subjects. Similarly, Kvetny et al [89] did not find a significant difference in BP when comparing 249 patients with SH and 963 patients with normal thyroid hormones and TSH [89]. In one of the studies called Rotterdam study, no difference in was detected regarding BP between 124 women with mild subclinical hypothyroidism

and 931 euthyroid women [24]. Previous studies revealed that the level of fasting glucose [90,91] and hemoglobin A1C [91] or prevalence of diabetes mellitus [81,92,93] did not differ between the subclinical hypothyroidism and euthyroid subjects. Goiter is twice among prevalent in patients with subclinical hypothyroidism [1] and it is found in 9.5% of our patients. The distribution of serum TSH values in the normal population is skewed, with the majority of individuals having TSH values at the lower end of the normal range [94]. Recent studies have reported that "high normal" TSH values may be associated with modest increases in serum cholesterol levels [95-97] and that serum cholesterol levels improve when TSH values are reduced from the high end to the low end of the normal range with L-thyroxine supplementation [95]. Furthermore, individuals with high normal serum TSH levels may have endothelial dysfunction [98]. Thus, although not based on prospective outcomes data, these findings would suggest to us that the optimal goal TSH range for L-thyroxine-treated patients is 0.5–2.0 μU/ml. Also some study conducted in America showed that treating as well as screening subclinical hypothyroidism in all people above the age of 35 years is cost effective as a lot of other similar screening modalities done for other diseases in the country[99]. Subclinical hypothyroidism is quite frequently encountered problem with patients ultimately ending up in gross hypothyroidism. Subjects with this problem have large number of somatic symptoms, deficits in areas related to memory, depressed mood, cardiac

problems like improper functioning of the heart in diastole and systole, increase in the amount of total lipid and low density lipoprotein predisposing the patient to the problem of landing him ultimately in atherosclerosis. There are large number studies which have demonstrated that many of these untoward problems can be cured or improved if the patients are adequately treated with L- thyroxine hormone. Also treating these patients with subclinical hypothyroidism is not a waste of cost compared to the benefits. It is advised that treatment should be given early in the disease even though the patients do not have symptoms because these patients eventually end up with the classical symptoms of severe hypothyroidism because the glands function gradually deteriorates particularly in those subjects who have antibodies against the thyroid who are more prone to develop hypothyroidism. Due to these reasons hormone therapy is advised for most of the subjects presenting with subclinical hypothyroidism with special importance to subjects presenting with symptoms, risk factors relating to the heart, goitres or having antibodies against the thyroid gland and in women patients diagnosed with pregnancy. In spite of the beneficial effects of treating these patients we have to determine how far these benefits carry an advantage over some of the risks associated with the therapy because data relating to the outcome are lacking and also there is a danger of over suppression of Thyroid stimulating hormone in those on hormone therapy. The potential consequences of untreated mild thyroid failure

on atherosclerosis in adults and on intellectual potential in infants born to mothers with mild thyroid failure begs for definitive answers about the therapeutic benefits of thyroid hormone replacement. It is no longer scientifically or morally justifiable to argue whether mild thyroid failure is something or nothing. What is clearly needed now are clean, randomized, prospective, and adequately powered trials to provide unequivocal answers to the lingering but critical questions regarding the effects of mild thyroid failure and its treatment on important end points such as intellectual function, ischemic heart disease, and quality of life.

Conclusion

• There is a high prevalence of subclinical hypothyroidism in elderly females above 50 years of age.

• Most of the patients with subclinical hypothyroidism have serum TSH below 10μIU/ml.

• Symptoms of hypothyroidisim was seen in patients with subclinical hypothyroidism. (28.57% of subjects in this study) Fatigability and Constipation were the most common symptoms.

• Subjects with subclinical hypothyroidism are more susceptible to ischemic heart disease.

• There is no increased susceptibility to develop diabetes mellitus and hypertension in subjects with subclinical hypothyroidism.

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APPENDIX

1	BMI	Body Mass Index	21	rT3	Reverse T3
2	D1	Type 1 deiodinase	22	RAIU	Radio Active Iodine Uptake
3	D2	Type 2 deiodinase	23	RXR	Retinoid X Receptor
4	DIT	Diiodothyronine	24	SH	Subclinical Hypothyroidism
5	DUOX	Dual Oxidase	25	SLC5A	Solute Carrier Family 5A
6	E	Embryonic Day	26	T3	Triiodothyronine
7	FSH	Follicle Stimulating Hormone	27	T4	Tetraiodothyronine
8	FT3I	Free T3 Index	28	TBAb	Thyroid Blocking Antibody
9	FT4I	Free T4 Index	29	TBG	Thyroid Binding Globulin
10	hCG	Human chorionic gonadotorpin	30	TgAb	Thyroglobulin Auto antibody
11	HDL	High Density Lipoprotein	31	THBR	Thyroid Hormone Binding Ratio
12	I	Iodine	32	THOX	Thyroid Hormone Oxidase
13	IHD	Ischemic Heart Disease	33	TPO	Thyroid Peroxidase
14	LDL	Low Density Lipoprotein	34	TPOAb	Thyroid Peroxidase Antibody
15	LH	Luteinizing Hormone	35	TR	Thyroid hormone Receptor
16	MCR	Metabolic Clearance Rate	36	TRH	Thyroid Releasing Hormone
17	MCT	Mono Carboxylate Anion Transporter	37	TSAb	Thyroid Stimulating Antibody
18	MIT	Mono Iodo Thyronine	38	TSH	Thyroid Stimulating Hormone
19	NIS	Sodium Iodide Symporter	39	TSHR	TSH Receptor
20	PVN	Para Ventricular Nucleus	40	TTR	Transthyretin

PROFORMA

NAME: ADDRESS:

AGE: SEX: OCCUPATION:

HISTORY OF:

1. FATIGABILITY
2. WEIGHT GAIN
3. CONSTIPATION
4. COLD INTOLERANCE
5. DRY SKIN
6. HOARSENESS
7. OTHER SYMPTOMS: SPECIFIED

PAST H/O:

1. SYSTEMIC HYPERTENSION
2. DIABETES MELLITUS
3. CORONARY HEART DISEASE
4. HYPOTHYROIDISM
5. DRUG INTAKE
6. EXPOSURE TO IRRADIATION

7. THYROID SURGERY

PERSONAL H/O:

1. MENSTRUAL HISTORY
2. OBSTRETIC HISTORY

CLINICAL EXAMINATION:

PULSE RATE: BLOOD PRESSURE: TEMPERATURE:

GOITRE:

CVS: RS:

ABDOMEN: CNS:

INVESTIGATIONS

1. FREE T3, FREE T4, TSH.
2. BLOOD SUGAR – FASTING AND POST PRANDIAL
3. ECG – RATE, RHYTHM, PR INTERVAL, AXIS, BUNDLE BRANCH BLOCK, ST-T CHANGES, CHAMBER ENLARGEMENT.
4. ECHO

Fig 1

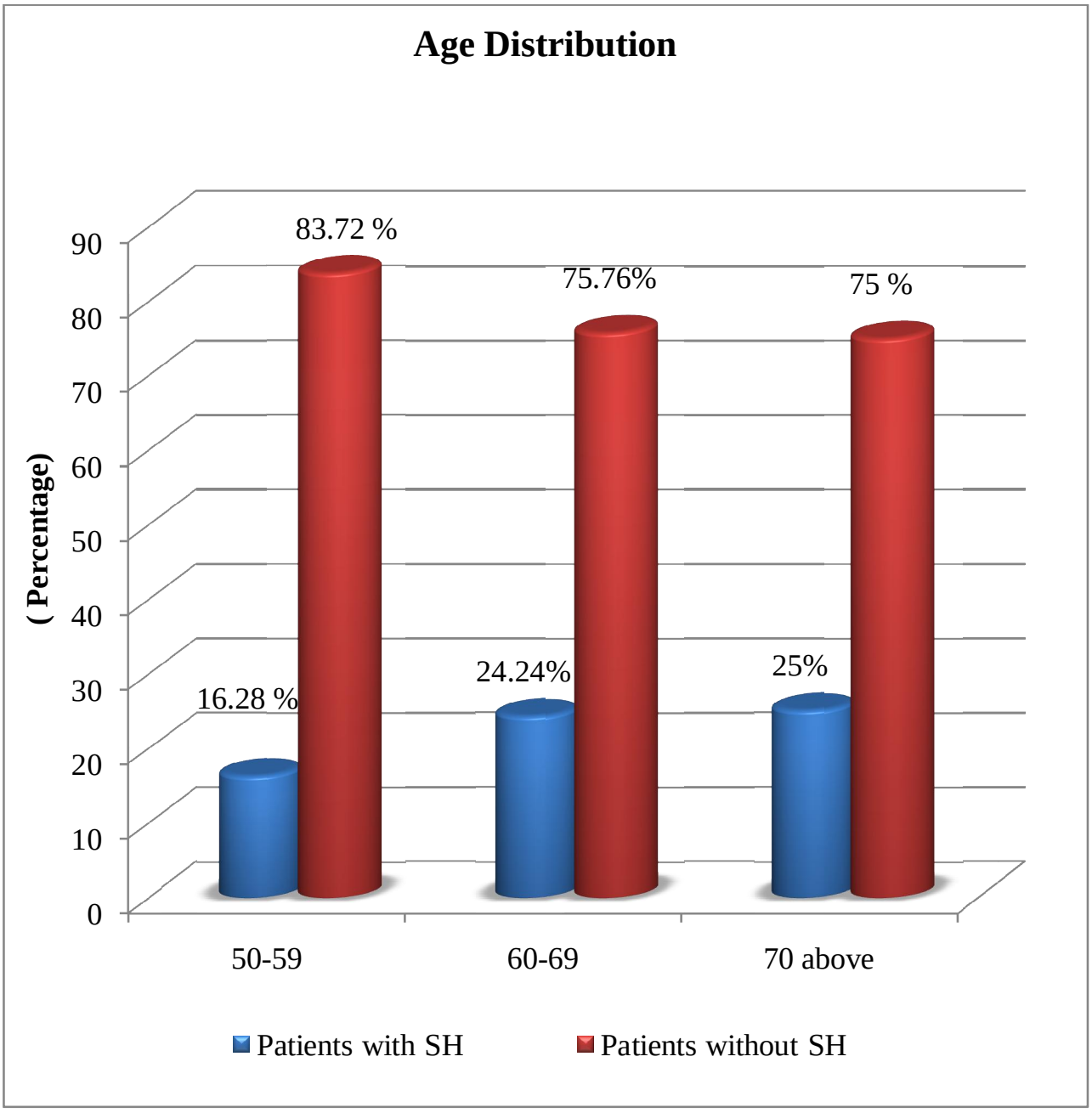

Age Distribution
(Percentage)
90
80
70
60
50
40
30
20
10
0
83.72 %
75.76%
75 %
16.28 %
24.24%
25%
50-59
60-69
70 above
Patients with SH
Patients without SH

Fig 2

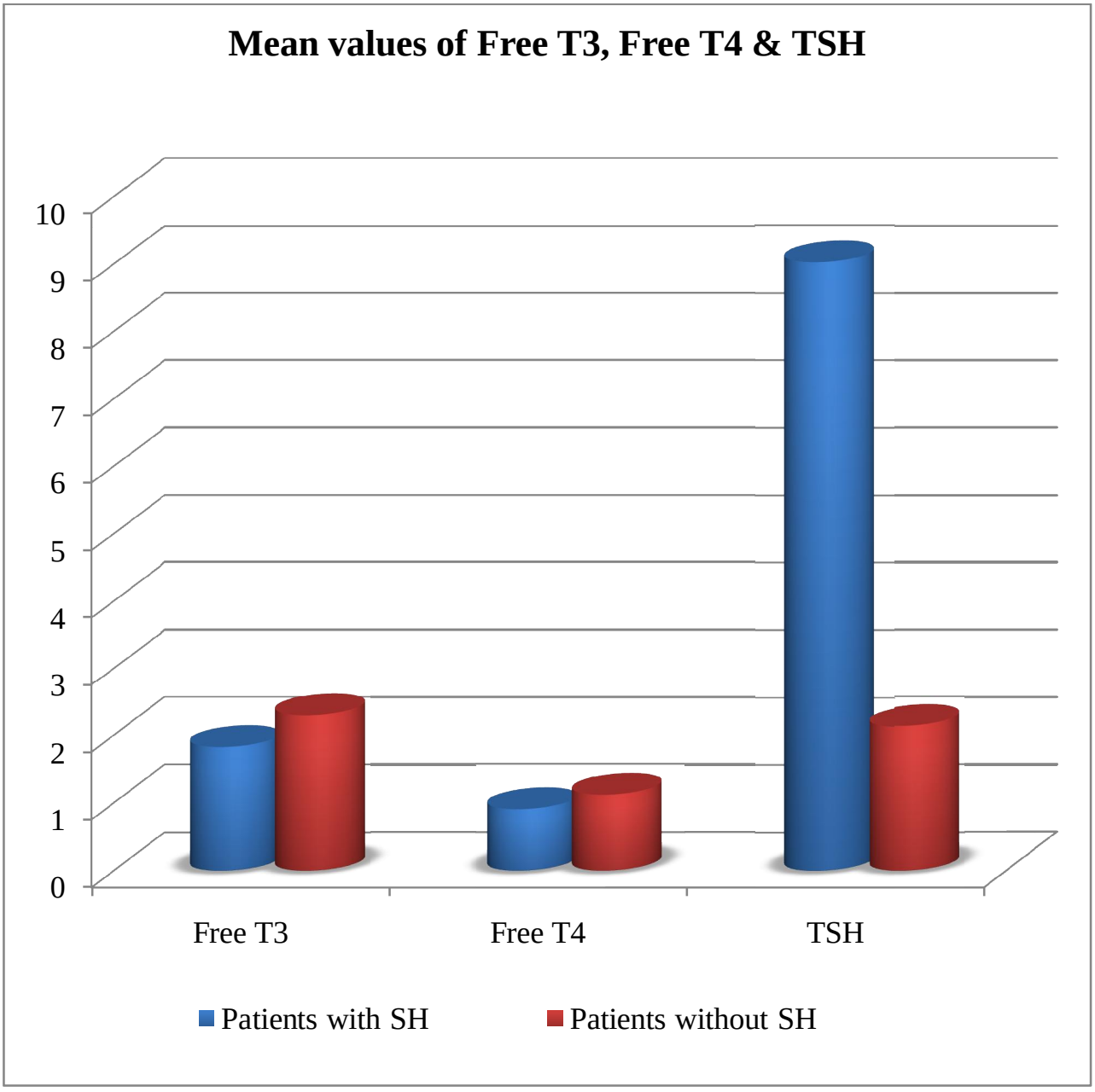

Mean values of Free T3, Free T4 & TSH
10
9
8
7
6
5
4
3
2
1
0
Free T3
Free T4
TSH
Patients with SH
Patients without SH

Fig 3

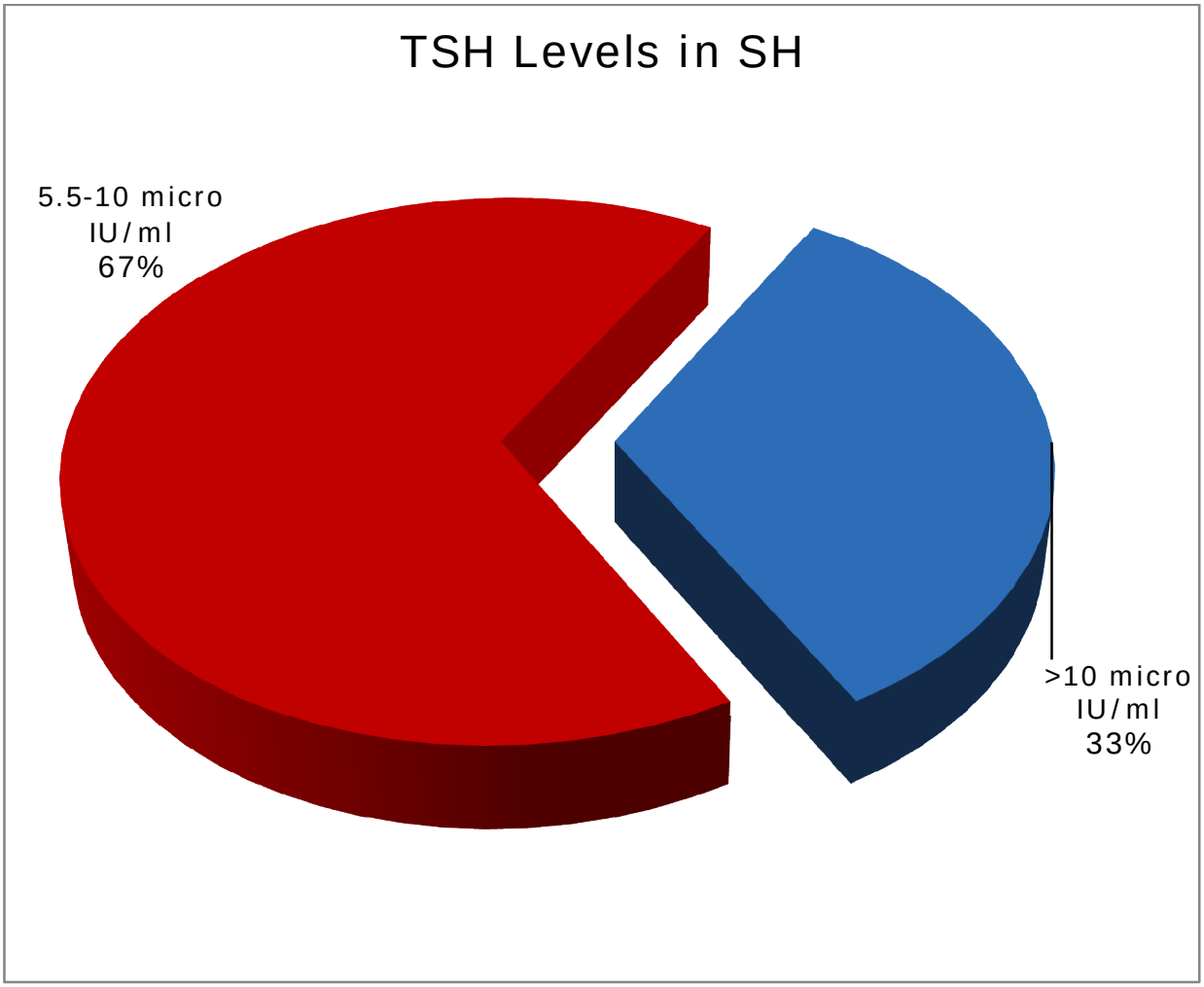


Fig 4

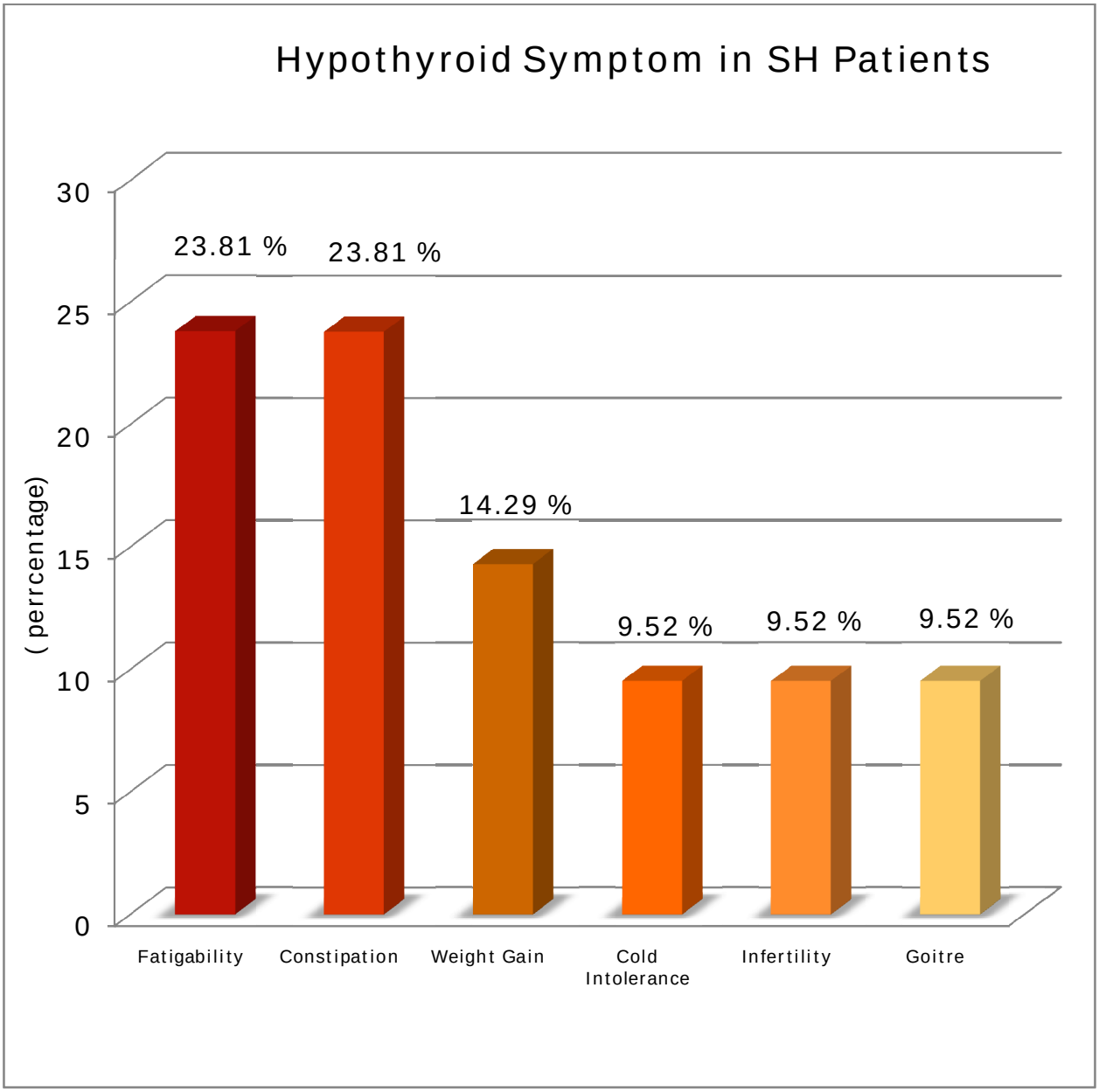
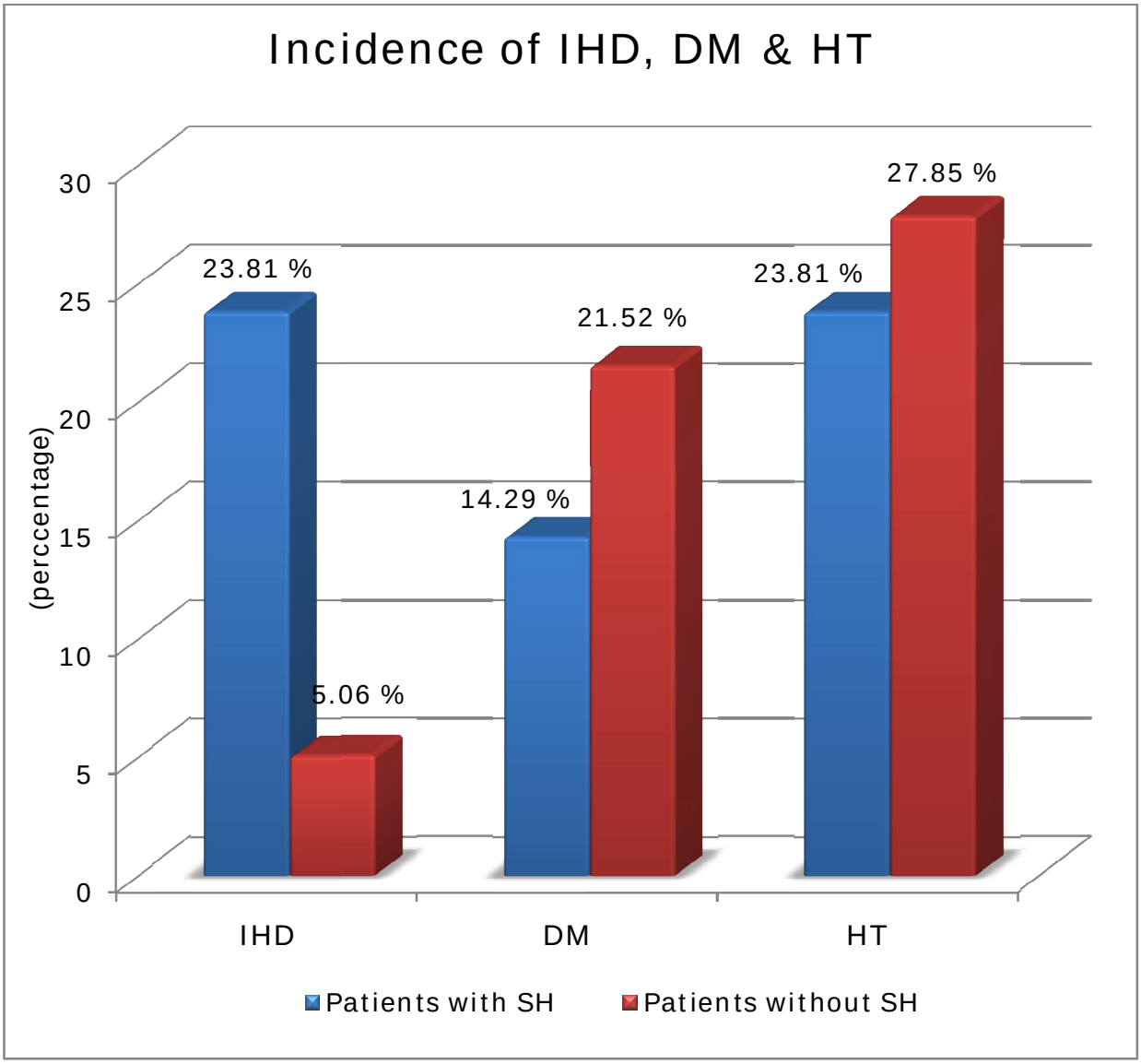

Hypothyroid Symptom in SH Patients
(perrcentage)
30
25
20
15
10
5
0
23.81 %
23.81 %
14.29 %
9.52 %
9.52 %
9.52 %
Fatigability
Constipation
Weight Gain
Cold Intolerance
Infertility
Goitre

Fig 5


Incidence of IHD, DM & HT
(perccentage)
30
25
20
15
10
5
0
23.81 %
5.06 %
14.29 %
21.52 %
23.81 %
27.85 %
IHD
DM
HT
Patients with SH
Patients without SH

MASTER CHART

S.NO	NAME	AGE (years)	OP.NO	FATIGABILITY	WEIGHT GAIN	CONSTIPATION	COLD INTOLERANCE	DRY SKIN	HOARSENESS	OTHER SYMPTOMS : SPECIFIED	GOITRE	PULSE RATE PER MINUTE	BLOOD PRESSURE mm/Hg	TEMPERATURE (Degree Fahrenheit)	FREE T3 (pg/mL)	FREE T4 (ng/dL)	TSH (mIU/mL)	BLOOD SUGAR - F, PP (mg/dL)	BLOOD UREA (mg/dL)	SERUM CREATININE (mg/dL)	ECG-EVIDENCE OF IHD	ECHO-EVIDENCE OF IHD
1	Lakshmi	51	983	No	No	No	No	No	No	No	No	72	120 / 70	98.3	2.56	1.22	1.7	88, 134	25	1	No	No
2	Thulasi	52	990	No	No	No	No	No	No	No	No	77	130 / 80	98.2	2.54	1.14	1.5	90, 140	30	0.9	Yes	Yes
3	Rani	52	1537	No	No	No	No	No	No	No	No	75	156 / 98	98.4	2.67	1.21	0.7	168, 310	33	0.9	No	No
4	Mangammal	53	1539	No	No	No	No	No	No	No	No	88	128 / 84	98.3	2.55	1.23	1	89, 128	34	0.8	No	No
5	Chandra	52	1543	No	No	No	No	No	No	No	No	85	126 / 82	98.5	1.98	0.93	7.9	88, 132	35	0.7	No	No
6	Kanchana	70	1550	No	No	No	No	No	No	No	Yes	70	130 / 70	98.1	2.86	1.36	1.3	87, 127	32	1	No	No
7	Rani	60	1605	No	No	No	No	No	No	No	No	90	134 / 84	98.4	2.72	1.38	1.2	84, 130	31	0.9	No	No
8	Pushpavalli	54	1666	No	No	No	No	No	No	No	No	71	162 / 104	98.5	2.63	1.25	2	78, 110	34	0.8	No	No
9	Parvathy	71	1834	No	No	No	No	No	No	No	No	79	136 / 86	98.3	1.92	0.92	9.2	74, 112	35	1.1	Yes	Yes
10	Paravatha	55	1900	No	No	No	No	No	No	No	No	80	126 / 74	98.4	2.58	1.32	1.7	85, 132	36	1.1	No	No
11	Kuppama	55	3172	No	No	No	No	No	No	No	No	86	110 / 70	98.2	2.27	1.08	1.4	88, 138	36	1	No	No
12	Sita	54	3222	No	No	No	No	No	No	No	No	92	120 / 80	98.1	2.25	1.09	1.3	142, 266	37	0.9	No	No
13	Raguvammal	72	3588	No	No	No	No	No	No	No	No	83	158 / 94	98.6	1.76	0.84	1.9	82, 150	37	0.9	No	No
14	Kannayi	70	3727	No	No	No	No	No	No	No	Yes	88	130 / 80	98.4	1.56	0.98	2	84, 146	38	0.8	No	No
15	Alamelu	61	3820	No	No	No	No	No	No	No	No	91	132 / 82	98.3	1.68	0.88	8.1	96, 132	25	1	No	No
16	Ponnatha	54	3831	No	No	No	No	No	No	No	No	77	134 / 86	98.3	2.1	0.86	3.5	88, 134	26	0.9	No	No
17	Krishnaveni	62	3837	No	No	No	No	No	No	No	No	75	148 / 96	98.6	2.02	0.92	3.2	138, 278	29	0.9	No	No
18	Kanagi	72	3840	No	No	No	No	No	No	No	No	73	130 / 80	98.2	1.81	0.86	4.4	86, 138	29	0.8	No	No
19	Kuttiyamma	65	3846	Yes	No	Yes	No	No	No	No	No	70	160 / 100	98.3	1.72	0.88	11	150, 305	30	0.8	No	No
20	Punitha	51	3850	No	No	No	No	No	No	No	No	75	128 / 76	98.4	1.85	0.89	3.9	88, 134	26	1	No	No
21	Paravatham	52	3872	No	No	No	No	No	No	No	No	87	158 / 94	98.4	2.29	1.09	1.1	95, 129	32	1.1	No	No
22	Prema	52	3888	No	No	No	No	No	No	No	No	83	136 / 76	98.5	2.28	1.12	1.1	96, 138	33	1	No	No
23	Pattamma	72	3916	Yes	Yes	Yes	Yes	No	No	Infertility	Yes	90	166 / 112	98.4	1.74	0.89	14	152, 298	36	0.9	Yes	Yes
24	Mekala	53	3920	No	No	No	No	No	No	No	No	79	128 / 78	98.3	1.78	0.86	7	82, 119	29	0.9	No	No
25	Vasantha	54	3928	No	No	No	No	No	No	No	No	73	130 / 84	98.3	2.21	1.05	0.7	84, 120	31	0.8	No	No

26	Jaya	56	3940	No	No	No	No	No	No	No	No	78	130 / 70	98.5	2.22	1.09	0.9	167, 289	33	1	No	No
27	Navaneetham	71	8043	No	No	No	No	No	No	No	No	86	166 / 110	98.4	2.18	1.04	2.9	88, 122	27	0.8	No	No
28	Jayabarathi	72	8050	No	No	No	No	No	No	No	No	85	134 / 88	98.4	1.88	0.92	1.1	145, 264	28	0.8	No	No
29	Anjalatchi	66	8075	No	No	No	No	No	No	No	No	81	132 / 86	98.3	2.46	1.17	1.4	90, 139	27	0.9	No	No
30	Anjanamma	62	8100	No	No	No	No	No	No	No	No	75	128 / 76	98.2	1.68	0.84	9.5	145, 284	30	1.1	No	No
31	Pushpa	55	8353	No	No	No	No	No	No	No	No	85	134 / 80	98.4	2.54	1.22	1.1	88, 110	34	1.1	No	No
32	Kala	54	8380	No	No	No	No	No	No	No	No	80	160 / 110	98.1	2.58	1.23	1	78, 110	34	1	No	No
33	Saroja	55	8616	No	No	No	No	No	No	No	No	79	132 / 78	98.2	2.42	1.22	1.3	99, 138	33	0.9	No	No
34	Usha	72	8617	No	No	No	No	No	No	No	No	87	130 / 80	98.4	1.61	0.81	8.2	100, 148	26	0.9	No	No
35	Sengani	63	8618	No	No	No	No	No	No	No	No	90	136 / 86	98.2	2.81	1.37	2.6	78, 111	28	0.8	No	No
36	Kalaiselvi	54	8632	No	No	No	No	No	No	No	No	77	134 / 84	98.3	1.95	0.93	7.2	80, 128	29	0.9	No	No
37	Ponnamma	74	8643	No	No	No	No	No	No	No	No	76	130 / 80	98.3	2.45	1.45	2.7	79, 96	33	1	No	No
38	Gengamma	63	8650	No	No	No	No	No	No	No	No	86	128 / 80	98.4	2.37	1.13	3.7	170, 322	32	0.9	No	No
39	Nagamma	71	8652	No	No	No	No	No	No	No	No	78	130 / 70	98.4	2.42	1.32	3.6	86, 127	31	0.9	No	No
40	Christina	54	8659	No	No	No	No	No	No	No	No	75	154 / 98	98.2	2.61	1.24	1.9	104, 145	28	0.8	No	No
41	Emarose	64	8668	No	No	No	No	No	No	No	No	88	110 / 70	98.4	1.85	0.89	9	111, 156	26	0.8	No	No
42	Sivagami	55	8682	No	No	No	No	No	No	No	No	74	110 / 80	98.5	2.02	0.99	1.1	91, 131	37	1	No	No
43	Vallimma	70	8690	No	No	No	No	No	No	No	No	73	134 / 86	98.3	2.04	0.97	1	94, 138	34	0.8	No	No
44	Paravayi	71	8691	No	No	No	No	No	No	No	No	89	160 / 100	98.4	2.12	1.48	2.7	165, 302	33	0.8	No	No
45	Chandra	56	8692	No	No	No	No	No	No	No	No	72	132 / 78	98.1	2.04	0.97	1	87, 135	28	0.8	No	No
46	Ganga	57	8699	No	No	No	No	No	No	No	Yes	86	134 / 86	98.2	2.05	1.05	2.3	88, 138	35	0.9	No	No
47	Jaya	59	10306	No	No	No	No	No	No	No	No	72	130 / 80	98.3	2.35	1.12	3.6	156, 279	36	1	No	No
48	Mallika	72	10310	No	No	No	No	No	No	No	No	87	158 / 98	98.4	2.84	1.35	1	98, 125	37	0.9	Yes	Yes
49	Kasthuri	65	10324	No	No	No	No	No	No	No	No	77	138 / 86	98.4	2.48	1.54	2.7	87, 123	38	0.9	No	No
50	Dayalu	54	10330	No	No	No	No	No	No	No	No	90	152 / 98	98.5	1.75	0.79	10	78, 110	27	0.8	Yes	Yes
51	Kanniyamma	64	10353	No	No	No	No	No	No	No	No	74	120 / 80	98.6	1.89	0.9	3.2	80, 120	26	0.9	No	No
52	Andal	53	10354	No	No	No	No	No	No	No	No	78	130 / 80	98.2	2.65	1.12	3.3	92, 110	28	0.9	No	No
53	Alamelu	70	10355	No	No	No	No	No	No	No	No	89	132 / 78	98.3	1.95	0.93	3.5	160, 288	30	0.8	No	No
54	Prathiba	65	10362	No	No	No	No	No	No	No	No	78	156 / 96	98.1	2.24	1.02	3.2	86, 108	32	1	No	No
55	Subathra	72	10370	No	No	No	No	No	No	No	No	74	134 / 78	98.1	1.86	0.96	7.8	89. 144	31	0.9	No	No
56	Pothayi	52	10375	No	No	No	No	No	No	No	No	82	132 / 84	98.3	2.08	0.99	1.2	74, 101	34	0.8	No	No
57	Rajeshwari	66	10384	Yes	Yes	Yes	No	No	No	No	No	88	158 / 96	98.4	1.74	0.79	11	76, 98	33	0.8	Yes	Yes
58	Thangammal	51	10390	No	No	No	No	No	No	No	No	79	110 / 80	98.2	2.04	0.99	1.8	88, 121	32	0.9	No	No
59	Saroja	67	13919	No	No	No	No	No	No	No	No	78	164 / 104	98.4	2.06	0.98	1.8	88, 124	31	1	No	No
60	Meena	68	13920	No	No	No	No	No	No	No	Yes	82	120 / 80	98.4	2.12	1.04	2.6	75, 101	29	0.8	No	No
61	Pottiammal	52	36138	No	No	No	No	No	No	No	No	85	134 / 86	98.5	1.92	0.99	6.8	78, 98	30	0.9	No	No
62	Kannatha	53	36777	No	No	No	No	No	No	No	No	88	130 / 80	98.2	2.39	1.14	3.2	78, 101	32	0.9	No	No
63	Thanammal	67	72554	No	No	No	No	No	No	No	No	76	130 / 70	98.4	2.21	1.05	3.1	86, 129	29	0.8	No	No
64	Thotiyamma	55	72555	No	No	No	No	No	No	No	No	77	170 / 110	98.3	2.01	0.95	2.8	92, 122	29	1	No	No
65	Kasthuri	73	72556	No	No	No	No	No	No	No	Yes	79	132 / 78	98.3	2.11	0.98	2.6	88, 122	37	0.9	No	No
66	Sathya	55	72557	No	No	No	No	No	No	No	No	89	134 / 80	98.4	1.98	1.11	7.5	90, 132	33	0.9	No	No

67	Sampoorna	68	72558	No	No	No	No	No	No	No	No	72	130 / 70	98.2	2.11	1.01	2.6	95, 128	33	0.8	No	No
68	Kuruvayi	60	72604	No	No	No	No	No	No	No	No	87	130 / 80	98.3	2.14	1.02	2.7	96, 132	34	0.8	No	No
69	Malliga	54	72607	No	No	No	No	No	No	No	No	78	134 / 80	98.5	2.84	1.35	2.8	79, 105	33	0.9	No	No
70	Lalitha	63	72611	No	No	No	Yes	No	No	Infertility	No	77	168 / 108	98.5	2.02	0.96	2.6	146, 268	26	0.9	No	No
71	Lakshmi	53	72618	No	No	No	No	No	No	No	No	77	130 / 78	98.3	2.04	0.97	2.5	82, 123	37	0.9	No	No
72	Sampoorani	64	72620	No	No	No	No	No	No	No	No	87	120 / 80	98.1	2.22	1.04	3.2	83, 113	35	0.8	No	No
73	Kuruvammal	74	72630	No	No	No	No	No	No	No	No	82	164 / 106	98.3	2.35	1.12	3.8	80, 132	35	1	No	No
74	Murugamma	53	72644	No	No	No	No	No	No	No	No	76	136 / 84	98.3	2.24	1.08	3.3	143, 269	34	0.9	No	No
75	Rosammal	53	72723	No	No	No	No	No	No	No	No	81	122 / 74	98.3	2.15	1.04	3.6	85, 118	35	0.9	No	No
76	Rani	66	76292	No	No	No	No	No	No	No	No	78	120 / 70	98.4	1.89	0.96	7.7	78, 100	33	0.8	No	No
77	Sathyavathi	52	76315	No	No	No	No	No	No	No	No	90	134 / 78	98.2	2.67	1.27	1.7	70. 101	32	0.9	No	No
78	Indira	67	76316	No	No	No	No	No	No	No	No	78	132 / 86	98.3	2.45	1.22	1.7	76, 105	33	0.9	No	No
79	Jayammal	53	76320	No	No	No	No	No	No	No	No	88	172 / 116	98.1	2.86	1.36	2.4	86, 118	31	0.8	No	No
80	Irusammal	62	76327	No	No	No	No	No	No	No	No	86	120 / 70	98.4	2.12	1.24	2.3	178, 320	30	1	No	No
81	Kannatha	61	76331	No	No	No	No	No	No	No	No	87	130 / 70	98.5	2.56	1.22	0.6	90, 136	33	1	No	No
82	Baby	72	80647	Yes	Yes	Yes	No	No	No	Infertility	Yes	73	168 / 114	98.2	1.76	0.78	12	94, 135	29	0.9	Yes	Yes
83	Chellayi	54	80650	No	No	No	No	No	No	No	No	71	132 / 78	98.3	2.47	1.12	0.7	166, 297	28	0.8	No	No
84	Ranganayaki	55	80751	No	No	No	No	No	No	No	No	81	168 / 108	98.4	2.42	1.15	1	96, 142	29	0.8	No	No
85	Theerthamal	71	80755	No	No	No	No	No	No	No	No	86	120 / 80	98.5	2.82	1.26	0.9	78, 98	34	0.9	Yes	Yes
86	Annammal	61	80792	No	No	No	No	No	No	No	No	87	136 / 86	98.3	2.12	1.01	1.5	94, 132	34	0.9	No	No
87	Sellammal	60	80793	No	No	No	No	No	No	No	No	85	156 / 94	98.4	2.15	1.02	1.3	92, 123	35	0.8	No	No
88	Selvi	61	80794	No	No	No	No	No	No	No	No	72	122 / 78	98.3	1.92	1.08	6.8	85, 116	29	0.9	No	No
89	Mangayi	72	80799	No	No	No	No	No	No	No	No	76	110 / 76	98.4	2.18	1.04	0.6	86, 107	28	0.9	No	No
90	Pattammal	62	80860	No	No	No	No	No	No	No	No	80	110 / 70	98.5	2.14	1.06	0.8	140, 286	29	0.9	No	No
91	Valarmathy	71	80868	No	No	No	No	No	No	No	No	78	162 / 104	98.4	1.83	0.87	3.6	98, 125	32	0.8	No	No
92	Nagammal	63	80870	No	No	No	No	No	No	No	No	74	134 / 78	98.4	2.22	1.15	4	144, 278	34	1	No	No
93	Nallatha	56	80888	No	No	No	Yes	No	No	No	No	88	130 / 80	98.3	1.75	0.83	10	72, 104	34	0.9	No	No
94	Sarojini	72	89361	No	No	No	No	No	No	No	No	76	130 / 70	98.4	2.05	0.98	6.9	97, 122	35	0.8	No	No
95	Rosayi	62	89365	No	No	No	No	No	No	No	No	70	154 / 96	98.4	2.21	1.05	3.5	92, 122	33	0.9	No	No
96	Dilliammal	61	89370	No	No	No	No	No	No	No	No	76	132 / 78	98.3	2.33	1.11	4	156, 298	34	0.9	No	No
97	Chellathayi	62	89379	No	No	No	No	No	No	No	No	89	120 / 70	98.5	2.01	0.95	1.9	98, 132	29	0.8	Yes	Yes
98	Chinnaponnu	53	89380	No	No	No	No	No	No	No	No	78	148 / 94	98.2	2.71	1.29	1	89, 127	29	0.8	No	No
99	Durga	63	89392	Yes	No	Yes	No	No	No	No	No	90	138 / 86	98.3	1.82	0.89	11	88, 120	32	0.8	No	No
100	Thinusammal	71	89395	No	No	No	No	No	No	No	No	88	156 / 98	98.4	2.98	1.42	1	134, 264	33	0.9	No	No